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Gases for establishing pneumoperitoneum during laparoscopic abdominal surgery (Review)

Yu T, Cheng Y, Wang X, Tu B, Cheng N, Gong J, Bai L

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TABLE OF CONTENTS

[Intervention Review]

Gases for establishing pneumoperitoneum during laparoscopic abdominal surgery

Tianwu Yu[1], Yao Cheng[2], Xiaomei Wang[2], Bing Tu[2], Nansheng Cheng[3], Jianping Gong[2], Lian Bai[4]

[1]Department of Hepatobiliary Surgery, Yongchuan Hospital, Chongqing Medical University, Chongqing, China. [2]Department of Hepatobiliary Surgery, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China. [3]Department of Bile Duct Surgery, West China Hospital, Sichuan University, Chengdu, China. [4]Department of Gastrointestinal Surgery, Yongchuan Hospital, Chongqing Medical University, Chongqing, China

Contact address: Lian Bai, Department of Gastrointestinal Surgery, Yongchuan Hospital, Chongqing Medical University, No. 439, Quxuanhua Road, Chongqing, 402160, China. bailian2016@sina.com.

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ABSTRACT

Background

This is an update of the review published in 2013.

Laparoscopic surgery is now widely performed to treat various abdominal diseases. Currently, carbon dioxide is the most frequently used gas for insufflation of the abdominal cavity (pneumoperitoneum). Although carbon dioxide meets most of the requirements for pneumoperitoneum, the absorption of carbon dioxide may be associated with adverse events. People with high anaesthetic risk are more likely to experience cardiopulmonary complications and adverse events, for example hypercapnia and acidosis, which has to be avoided by hyperventilation. Therefore, other gases have been introduced as alternatives to carbon dioxide for establishing pneumoperitoneum.

Objectives

To assess the safety, benefits, and harms of different gases (i.e. carbon dioxide, helium, argon, nitrogen, nitrous oxide, and room air) used for establishing pneumoperitoneum in participants undergoing laparoscopic general abdominal or gynaecological pelvic surgery.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 9), Ovid MEDLINE (1950 to September 2016), Ovid Embase (1974 to September 2016), Science Citation Index Expanded (1970 to September 2016), Chinese Biomedical Literature Database (CBM) (1978 to September 2016), ClinicalTrials.gov (September 2016), and World Health Organization International Clinical Trials Registry Platform (September 2016).

Selection criteria

We included randomised controlled trials (RCTs) comparing different gases for establishing pneumoperitoneum in participants (irrespective of age, sex, or race) undergoing laparoscopic abdominal or gynaecological pelvic surgery under general anaesthesia.

Data collection and analysis

Two review authors identified the trials for inclusion, collected the data, and assessed the risk of bias independently. We performed the meta-analyses using Review Manager 5. We calculated risk ratio (RR) for dichotomous outcomes (or Peto odds ratio for very rare outcomes), and mean difference (MD) or standardised mean difference (SMD) for continuous outcomes with 95% confidence intervals (CI). We used GRADE to rate the quality of evidence,

Main results

We included nine RCTs, randomising 519 participants, comparing different gases for establishing pneumoperitoneum: nitrous oxide (three trials), helium (five trials), or room air (one trial) was compared to carbon dioxide.

Three trials randomised participants to nitrous oxide pneumoperitoneum (100 participants) or carbon dioxide pneumoperitoneum (96 participants). None of the trials was at low risk of bias. There was insufficient evidence to determine the effects of nitrous oxide and carbon dioxide on cardiopulmonary complications (RR 2.00, 95% CI 0.38 to 10.43; two studies; 140 participants; very low quality of evidence), or surgical morbidity (RR 1.01, 95% CI 0.18 to 5.71; two studies; 143 participants; very low quality of evidence). There were no serious adverse events related to either nitrous oxide or carbon dioxide pneumoperitoneum (three studies; 196 participants; very low quality of evidence). We could not combine data from two trials (140 participants) which individually showed lower pain scores (a difference of about one visual analogue score on a scale of 1 to 10 with lower numbers indicating less pain) with nitrous oxide pneumoperitoneum at various time points on the first postoperative day, and this was rated asvery low quality .

Four trials randomised participants to helium pneumoperitoneum (69 participants) or carbon dioxide pneumoperitoneum (75 participants) and one trial involving 33 participants did not state the number of participants in each group. None of the trials was at low risk of bias. There was insufficient evidence to determine the effects of helium or carbon dioxide on cardiopulmonary complications (RR 1.46, 95% CI 0.35 to 6.12; three studies; 128 participants; very low quality of evidence) or pain scores (visual analogue score on a scale of 1 to 10 with lower numbers indicating less pain; MD 0.49 cm, 95% CI -0.28 to 1.26; two studies; 108 participants; very low quality of evidence). There were three serious adverse events (subcutaneous emphysema) related to helium pneumoperitoneum (three studies; 128 participants; very low quality of evidence).

One trial randomised participants to room air pneumoperitoneum (70 participants) or carbon dioxide pneumoperitoneum (76 participants). The trial was at unclear risk of bias. There were no cardiopulmonary complications or serious adverse events observed related to either room air or carbon dioxide pneumoperitoneum (both outcomes very low quality of evidence). The evidence of lower hospital costs and reduced pain during the first postoperative day with room air pneumoperitoneum compared with carbon dioxide pneumoperitoneum (a difference of about one visual analogue score on a scale of 1 to 10 with lower numbers indicating less pain, was rated as very low quality of evidence.

Authors' conclusions

The quality of the current evidence is very low. The effects of nitrous oxide and helium pneumoperitoneum compared with carbon dioxide pneumoperitoneum are uncertain. Evidence from one trial of small sample size suggests that room air pneumoperitoneum may decrease hospital costs in people undergoing laparoscopic abdominal surgery. The safety of nitrous oxide, helium, and room air pneumoperitoneum has yet to be established.

Further trials on this topic are needed, and should compare various gases (i.e. nitrous oxide, helium, argon, nitrogen, and room air) with carbon dioxide under standard pressure pneumoperitoneum with cold gas insufflation for people with high anaesthetic risk. Future trials should include outcomes such as complications, serious adverse events, quality of life, and pain.

PLAIN LANGUAGE SUMMARY

Different gases for insufflation of the abdominal cavity during key-hole abdominal surgery

Review question

What are the benefits and harms of various gases for insufflation (inflation with gas) of the abdominal (tummy) cavity to allow easier access to organs during laparoscopic (key-hole) abdominal surgery?

Background

Laparoscopic (key hole) surgery is now widely performed to treat various abdominal diseases. An ideal gas for insufflation of the abdominal cavity, increasing working and viewing space, should be cheap, colourless, not flammable, inexplosive, easily removed by the body, and completely non-toxic to participants. Currently, carbon dioxide is the most frequently used gas for this purpose. However, use of carbon dioxide may cause heart or lung complications. So, other gases have been suggested as alternatives to carbon dioxide.

Study characteristics

We searched for all relevant studies up to September 2016. We identified nine clinical trials with 519 participants, of which three trials (196 participants) compared nitrous oxide (laughing gas) with carbon dioxide, five trials (177 participants) compared helium with carbon dioxide, and one trial (146 participants) compared room air with carbon dioxide. Studies were conducted in the USA, Australia, China, Finland, and Netherlands. The age of the participants in the trials ranged from 19 to 62 years.

Key results

We are uncertain as to whether there are differences in the number of people with heart or lung complications or surgical complications between nitrous oxide and carbon dioxide. We are uncertain as to whether there are any differences in heart or lung complications, surgical complications, or pain scores between helium and carbon dioxide.

There were no serious side effects related to the use of carbon dioxide, nitrous oxide, or room air, but generally serious side effects are rare events and it would take larger studies with many more participants to be sure that these gases are equally safe. There were three serious side effects when helium was used. Room air seemed to be associated with lower total hospital costs compared with carbon dioxide for insufflation of the abdominal cavity.

Because of the few participants included in the review, the safety of using nitrous oxide, helium, or room air is unknown. There is no evidence for any clinical improvement by using nitrous oxide, helium, or room air instead of carbon dioxide.

Quality of the evidence

Overall, the quality of the evidence for the results is very low. Thus, future well-designed trials examining complications, harms, quality of life, and pain are urgently needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Nitrous oxide versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

Nitrous oxide versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

Patient or population: people undergoing laparoscopic general abdominal or gynaecological pelvic surgery under general anaesthesia

Setting: secondary and tertiary care

Intervention: nitrous oxide pneumoperitoneum

Comparison: carbon dioxide pneumoperitoneum

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with carbon dioxide pneumoperitoneum	Risk with nitrous oxide pneumoperitoneum				
Cardiopulmonary complications Follow-up: 0 to 1 month	29 per 1000	57 per 1000 (11 to 302)	**RR 2.00** (0.38 to 10.43)	140 (2 studies)	⊕⊖⊖⊖ **Very low** [1,2]	Trial sequential analysis showed a diversity-adjusted required information size of 3781 participants to support or refute nitrous oxide pneumoperitoneum.
Procedure-related general complications Follow-up: 0 to 1 month	28 per 1000	28 per 1000 (5 to 160)	**RR 1.01** (0.18 to 5.71)	143 (2 studies)	⊕⊖⊖⊖ **Very low** [1,2]	Trial sequential analysis showed a diversity-adjusted required information size of 3919 participants to support or refute nitrous oxide pneumoperitoneum.
Pneumoperitoneum-related serious adverse events Follow-up: 0 to 1 month	See comment	See comment	Not estimable	196 (3 studies)	⊕⊕⊖⊖ **Low** [3,4]	None of the studies reported any pneumoperitoneum-related serious adverse events.
Mortality Follow-up: 0 to 1 month	See comment	See comment	Not estimable	196 (3 studies)	⊕⊕⊖⊖ **Low** [3,4]	None of the studies reported any deaths.
Quality of life	None of the studies reported quality of life.					
Pain scores (first postoperative day)	See comment	See comment	Not estimable	140 (2 studies)	⊕⊖⊖⊖ **Very low** [3,4,5]	Neither trials reported the standard deviation for pain scores on the VAS scale.

VAS, lower score indicates less pain. Scale: 0 cm to 10 cm Follow-up: 1 day						Substantial clinical heterogeneity in between the 2 studies.
Analgesia requirements Follow-up: 1 week	The mean analgesia requirement in the carbon dioxide pneumoperitoneum was 54.4 mg of oxycodone and 2.0 tablets/24 hours of ibuprofen	The mean analgesia requirement in the nitrous oxide pneumoperitoneum was **0.69 standard deviations lower** (1.42 lower to 0.04 higher)	**SMD -0.69** (-1.42 to 0.04)	193 (3 studies)	⊕⊖⊖⊖ **Very low** [3,4,6]	-
Hospital costs	None of the studies reported costs.					

*The basis for the **assumed risk** is the mean comparison group proportion in the studies. **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for very serious risk of bias.
[2] Downgraded one level for serious imprecision (the confidence interval of risk ratio overlapped 0.75 and 1.25, and small sample size).
[3] Downgraded one level for serious imprecision (small sample size).
[4] Downgraded one level for serious risk of bias.
[5] Downgraded one level for indirectness.
[6] Downgraded one level for severe inconsistency (substantial heterogeneity as indicated by the I^2 statistic).

Summary of findings 2. Helium versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

Helium versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

Patient or population: people undergoing laparoscopic general abdominal or gynaecological pelvic surgery under general anaesthesia

Setting: secondary and tertiary care

Intervention: helium pneumoperitoneum

Comparison: carbon dioxide pneumoperitoneum

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with carbon dioxide pneumoperitoneum	Risk with helium pneumoperitoneum				
Cardiopulmonary complications Follow-up: 0 to 1 month	30 per 1000	44 per 1000 (10 to 183)	**RR 1.46** (0.35 to 6.12)	128 (3 studies)	⊕⊖⊖⊖ **Very low** [1,2]	Trial sequential analysis showed a diversity-adjusted required information size of 3651 participants to support or refute helium pneumoperitoneum.
Procedure-related general complications Follow-up: 0 to 1 month	See comment	See comment	Not estimable	144 (4 studies)	⊕⊖⊖⊖ **Very low** [3,4]	None of the studies reported any significant procedure-related general complications in either group.
Pneumoperitoneum-related serious adverse events Follow-up: 0 to 1 month	0 per 1000	44 per 1000 (0 to 0)	**Peto OR** 8.28 (0.86 to 80.03)	128 (3 studies)	⊕⊖⊖⊖ **Very low** [1,3,5]	Trial sequential analysis showed a diversity-adjusted required information size of 4793 participants to support or refute helium pneumoperitoneum.
Mortality Follow-up: 0 to 1 month	See comment	See comment	Not estimable	144 (4 studies)	⊕⊕⊖⊖ **Low** [1,3]	None of the studies reported any deaths.
Quality of life	None of the studies reported quality of life.					
Pain scores (first postoperative day) Visual analogue scale, lower score indicates less pain. Scale: 0 to 10 Follow-up: 1 day	The mean pain scores (first postoperative day) in the carbon dioxide pneumoperitoneum was 3.01 cm	The mean pain scores (first postoperative day) in the helium pneumoperitoneum was **0.49 cm higher** (0.28 lower to 1.26 higher)	**MD 0.49** (-0.28 to 1.26)	108 (2 studies)	⊕⊖⊖⊖ **Very low** [1,3,5]	-

Analgesia requirements (morphine mg) Follow-up: 2 days	The mean analgesia requirements (morphine) in the carbon dioxide pneumoperitoneum was 36.6 mg	The mean analgesia requirements (morphine) in the helium pneumoperitoneum was **12 mg higher** (4.44 higher to 19.56 higher)	**MD 12.00** (4.44 to 19.56)	90 (1 study)	⊕⊖⊖⊖ **Very low** [1,3,5]	-
Hospital costs	None of the studies reported costs.					

*The basis for the **assumed risk** is the mean comparison group proportion in the studies. **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded one level for serious risk of bias.
[2] Downgraded two levels for very serious imprecision (the confidence interval of risk ratio overlapped 0.75 and 1.25, and small sample size).
[3] Downgraded one level for serious imprecision (small sample size).
[4] Downgraded two levels for very serious risk of bias.
[5] Downgraded one level for indirectness.

Summary of findings 3. Room air versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

Room air versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

Patient or population: people undergoing laparoscopic general abdominal or gynaecological pelvic surgery under general anaesthesia

Setting: secondary and tertiary care

Intervention: room air pneumoperitoneum

Comparison: carbon dioxide pneumoperitoneum

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments

	Risk with carbon dioxide pneumoperitoneum	Risk with room air pneumoperitoneum				
Cardiopulmonary complications Follow-up: 1 month	See comment	See comment	Not estimable	146 (1 study)	⊕⊖⊖⊖ **Very low** [1,2]	Trial did not report any cardiopulmonary complications.
Procedure-related general complications	The study did not report procedure-related general complications.					
Pneumoperitoneum-related serious adverse events Follow-up: 1 month	See comment	See comment	Not estimable	146 (1 study)	⊕⊖⊖⊖ **Very low** [1,2]	Trial did not report any pneumoperitoneum-related serious adverse events.
Mortality Follow-up: 1 month	See comment	See comment	Not estimable	146 (1 study)	⊕⊕⊖⊖ **Low** [2,3]	The study did not report any deaths.
Quality of life	The study did not report quality of life.					
Pain scores (first postoperative day) Visual analogue scale, lower score indicates less pain. Scale: 0 to 10 cm Follow-up: 1 day	The mean pain scores (first postoperative day) in the carbon dioxide pneumoperitoneum was 2.60 cm	The mean pain scores (first postoperative day) in the room air pneumoperitoneum was **0.80 cm lower** (1.15 lower to 0.45 lower)	**MD -0.80** (-1.15 to -0.45)	146 (1 study)	⊕⊖⊖⊖ **Very low** [1,2]	-
Analgesia requirements	The study did not report analgesia requirements.					
Hospital costs (CNY) Follow-up: 1 month	The mean hospital costs in the carbon dioxide pneumoperitoneum was CNY12,012.00	The mean hospital costs in the room air pneumoperitoneum was **CNY2667.00 lower** (3275.68 lower to 2058.32 lower)	**MD -2667.00** (-3275.68 to -2058.32)	146 (1 study)	⊕⊖⊖⊖ **Very low** [1,2]	-

*The basis for the **assumed risk** is the mean comparison group proportion in the studies. **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded two levels for very serious risk of bias.
[2] Downgraded one level for serious imprecision (small sample size).
[3] Downgraded one level for serious risk of bias.

BACKGROUND

Description of the condition

Laparoscopic surgery, which was originally developed in the 1910s, is now widely performed by general surgeons to treat various abdominal diseases (Ahmad 2015; Antoniou 2015; Birch 2016; Cheng 2013; Spaner 1997), including diseases of the stomach, gallbladder, liver, pancreas, spleen, intestine, and kidney (Best 2016; Cai 2014; Cheng 2012a; Cheng 2015; Cheng 2016; Dasari 2011; Keus 2006; Kuhry 2008; Nabi 2016; Rao 2013; Riviere 2016; Sanabria 2013; Sauerland 2010).

The exact number of people undergoing laparoscopic surgery each year worldwide is unknown. Laparoscopic surgery offers various advantages over conventional open surgery, including less postoperative pain, smaller scars, shorter hospital stay, and a quicker recovery (Ahmad 2015; Antoniou 2015; Birch 2016). This method has become the gold standard for some abdominal procedures (e.g. laparoscopic cholecystectomy) (Gurusamy 2014; Keus 2006).

Description of the intervention

The first step in laparoscopic surgery is the establishment of pneumoperitoneum, including entry into the abdominal cavity and then insufflation of air or gas (Ahmad 2015; Birch 2016; Cheng 2013; Gurusamy 2014; Neudecker 2002), for facilitating adequate working and viewing space. Two common entry techniques are used: an open method (all layers of the abdominal wall are incised, and a trocar is inserted under direct vision), and a closed method (only the skin is incised, and a Veress needle is then inserted blindly into the abdominal cavity) (Ahmad 2015; Cheng 2013; Neudecker 2002). After entry into the abdominal cavity, gas is insufflated through the trocar (open method) or the Veress needle (closed method) to separate the abdominal wall from the internal organs (Ahmad 2015; Cheng 2013; Gurusamy 2014; Neudecker 2002). The established pneumoperitoneum provides sufficient operating space to ensure adequate visualisation of camera and manipulation of instruments in the abdominal cavity (Cheng 2013; Gurusamy 2014; Neudecker 2002).

How the intervention might work

A pneumoperitoneum of 8 mmHg to 20 mmHg is created and pressure is maintained during laparoscopic surgery (Gurusamy 2014; Karapolat 2011; Neudecker 2002). The ideal gas for establishing pneumoperitoneum should be cheap, colourless, non-flammable, non-explosive, easily excreted, and completely non-toxic to participants (Menes 2000; Neuhaus 2001; Sammour 2009). Carbon dioxide, which was introduced to create pneumoperitoneum in 1920s, is the most common gas used for insufflation currently (Cheng 2012b; Karapolat 2011; Neudecker 2002; Spaner 1997). Carbon dioxide is absorbed by the peritoneum, delivered directly to the lungs by the circulation (Eaton 2009; Grabowski 2009), and is excreted by the lungs during respiratory exchange (Eaton 2009; Neuhaus 2001). Although carbon dioxide meets most of the requirements (e.g. low cost, non-flammable, chemically stabile, and with high diffusion capacity with subsequent rapid absorption and excretion), it is not a perfect gas. The absorption of carbon dioxide causes hypercapnia and acidosis, which has to be avoided by hyperventilation (Grabowski 2009; Gurusamy 2014; Neudecker 2002). It is associated with various cardiopulmonary (heart and lung) complications, such as tachycardia, cardiac arrhythmias, and pulmonary oedema (Gurusamy 2014; Gutt 2004; Kwak 2010; Neudecker 2002). In addition, it may cause postoperative pain due to peritoneal irritation, and its use is associated with immunological impairment (Grabowski 2009; Neuhaus 2001). Elderly people with cardiopulmonary diseases are more likely to experience these adverse events (Grabowski 2009; Karapolat 2011).

Identifying an ideal insufflation gas to replace carbon dioxide attracts the attention of some researchers in the era of laparoscopic surgery (Menes 2000; Neuhaus 2001). Various gases, such as helium, argon, nitrogen, nitrous oxide, and room air, have been introduced as alternatives to carbon dioxide to establish pneumoperitoneum (Gardner 1995; Karapolat 2011; Menes 2000; Neuhaus 2001; Rammohan 2011). However, their uses are controversial. Helium and argon are inert gases that may offer some advantages over carbon dioxide (Gutt 2004; Menes 2000; Neuhaus 2001). Nevertheless, they are less soluble than carbon dioxide, which might increase the risk of venous gas embolism (Gutt 2004; Menes 2000; Neuhaus 2001). Nitrous oxide, also known as laughing gas, is a mild anaesthetic (Aboumarzouk 2011). It may reduce postoperative pain theoretically because of its anaesthetic and analgesic properties (Rammohan 2011; Tsereteli 2002). However, there have been two cases of explosion using electrocautery during laparoscopy (El-Kady 1976; Gunatilake 1978), and the risk of explosion when using nitrous oxide insufflation remains controversial (Hunter 1995; Neuman 1993; Rammohan 2011).

Why it is important to do this review

The first version of this review was published in 2013 (Cheng 2013). Further randomised controlled trials (RCTs) evaluating different gases for establishing pneumoperitoneum during laparoscopic abdominal surgery have been published since the review, and these studies have now been assessed for inclusion and presented in this update.

OBJECTIVES

To assess the safety, benefits, and harms of different gases (e.g. carbon dioxide, helium, argon, nitrogen, nitrous oxide, room air) used for establishing pneumoperitoneum in participants undergoing laparoscopic general abdominal or gynaecological pelvic surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs (irrespective of sample size, language, or publication status) comparing different gases used for establishing pneumoperitoneum in participants undergoing laparoscopic abdominal surgery under general anaesthesia. We excluded studies on participants undergoing laparoscopic abdominal surgery under local/regional anaesthesia. We excluded quasi-randomised trials (in which the allocation was performed on the basis of a pseudo-random sequence, e.g. odd/even hospital number or date of birth, alternation), cluster randomised trials, and non-randomised studies.

Types of participants

Participants (irrespective of age, sex, or race) who had undergone laparoscopic abdominal or gynaecological pelvic surgery (irrespective of elective or emergency procedure) under general anaesthesia.

Types of interventions

We included laparoscopic abdominal surgeries performed under standard pressure (12 mmHg to 16 mmHg) pneumoperitoneum with cold gas insufflation (Gurusamy 2014). We planned to assess the following gases for establishing pneumoperitoneum.

- Nitrous oxide versus carbon dioxide.
- Helium versus carbon dioxide.
- Room (ambient) air versus carbon dioxide.
- Argon versus carbon dioxide.
- Nitrogen versus carbon dioxide.
- Any other gas versus carbon dioxide.
- Any other gas (except carbon dioxide) versus any other gas (except carbon dioxide).

Types of outcome measures

Primary outcomes

- Complications (time point closest to 30 days; defined and graded by the Clavien-Dindo complications classification system) (Clavien 2009).
  - Cardiopulmonary complications (defined by authors, e.g. arrhythmia, ischaemias, atelectasis, hypoxaemia, pneumothorax, pulmonary oedema).
  - Procedure-related general complications (surgical morbidity).
- Pneumoperitoneum-related serious adverse events (time point closest to 30 days; defined by authors, e.g. gas embolism, subcutaneous emphysema, abdominal explosion).

Secondary outcomes

- Mortality (up to 30 days postoperatively).
- Quality of life (30 days, any validated score).
- Pain scores (time point closest to seven days postoperatively; graded by visual analogue score (VAS) scale (e.g. 0 cm to 10 cm)).
- Analgesia requirements (time point closest to seven days).
- Costs (time point closest to 30 days; e.g. costs of gases, hospital costs).
- Cardiopulmonary changes (time point closest to seven days; defined by authors, e.g. heart rate, blood pressure, blood pH, cardiac output, pulmonary compliance, peak airway pressure).

Search methods for identification of studies

We designed the search strategy with the help of Sys Johnsen (Cochrane Information Specialist of the Cochrane Colorectal Cancer Group). Searches were conducted in September 2016 irrespective of language, year, or publication status.

Electronic searches

We searched the following electronic databases with no language or date of publication restrictions:

- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library) (2016, Issue 9) (Appendix 1);
- MEDLINE (Ovid) (1950 to September 2016) (Appendix 2);
- Embase (Ovid) (1974 to September 2016) (Appendix 3);
- Science Citation Index Expanded (Web of Science) (1970 to September 2016) (Appendix 4);
- World Health Organization International Trials Registry Platform search portal (apps.who.int/trialsearch/) (September 2016);
- ClinicalTrials.gov (www.clinicaltrials.gov/) (September 2016);
- Chinese Biomedical Literature Database (CBM) (1978 to September 2016).

Searching other resources

Furthermore, we also searched the following databases in September 2016:

- Current Controlled Trials (www.controlled-trials.com/);
- Chinese Clinical Trial Register (www.chictr.org/);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

We also searched the reference lists of identified studies and meeting abstracts via the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) (www.sages.org/), European Association for Endoscopic Surgery (EAES) (www.eaes-eur.org/), and Conference Proceedings Citation Index to explore further relevant clinical trials. We planned to communicate with the authors of RCTs that were included for further information in the review.

Data collection and analysis

We conducted the systematic review according to guidelines of the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011a) and *Cochrane Colorectal Cancer Group Module* (Andersen 2015).

Selection of studies

After completing the searches, we merged the search results using the software package Endnote X5 (reference management software) and removed duplicate records. Two review authors (WX, TB) independently scanned the title and abstract of every record identified by the search for inclusion. We retrieved the full text for further assessment if the inclusion criteria were unclear from the abstract. We included eligible studies irrespective of whether they reported the measured outcome data. We detected duplicate publications by identifying common authors, centres, details of the interventions, numbers of participants, and baseline data (Higgins 2011b). We excluded papers that did not meet the inclusion criteria and listed the reasons for their exclusion. A third review author (YT) resolved any discrepancy between the two authors by discussion.

Data extraction and management

We used a standard data collection form for study characteristics and outcome data, which had been piloted on at least one study in the review. Two review authors (CN, GJ) extracted the following study characteristics from included studies:

- methods: study design, total duration study and run in, number of study centres and location, study setting, withdrawals, date of study;

- participants: number of participants, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria;
- interventions: intervention, comparison;
- outcomes: primary and secondary outcomes specified and collected, time points reported;
- notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (CN, GJ) independently extracted outcome data from included studies. We resolved disagreements by consensus or by involving a third review author (YT). One review author (CN) copied across the data from the data collection form into Review Manager 5 (RevMan 2014). We double-checked that the data were entered correctly by comparing the study reports with how the data were presented in the systematic review. A second review author (BL) cross-checked study characteristics for accuracy against the trial reports.

Assessment of risk of bias in included studies

Two review authors (WX, TB) independently assessed the risk of bias in the included trials, using the Cochrane 'Risk of bias' tool (Chapter 8, Higgins 2011c). We assessed risk of bias for the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective reporting bias;
- other sources of bias (baseline imbalances).

We judged each domain as low risk, high risk, or unclear risk of bias according to the criteria used in the Cochrane 'Risk of bias' tool (see Appendix 5) (Chapter 8.5.d, Higgins 2011c). We considered a trial to be at low risk of bias if we assessed the trial as at low risk of bias across all domains. Otherwise, we considered trials at unclear risk of bias or at high risk of bias regarding one or more domains as at high risk of bias. We resolved any difference in opinion by discussion. In case of disagreements, consensus was reached by discussion with a third review author (CY).

We presented the results of the risk of bias in two figures (a 'Risk of bias' graph and a 'Risk of bias' summary) generated by Review Manager 5 (RevMan 2014).

Measures of treatment effect

We performed the meta-analysis using Review Manager 5 (RevMan 2014). For dichotomous outcomes, we calculated risk ratio (RR) with 95% confidence interval (CI) (Deeks 2011). In case of rare events (e.g. mortality, serious adverse events), we calculated the Peto odds ratio (Peto OR) (Deeks 2011). For continuous outcomes, we calculated the mean difference (MD) with 95% CI (Deeks 2011). For continuous outcomes with different measurement scales in different RCTs, we calculated the standardised mean difference (SMD) with 95% CI (Deeks 2011).

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We contacted the original investigators to request further information in case of missing data. If there was no reply, we used only the available data in the analyses. We also performed 'best-case'/'worst-case' scenario analyses to take into account missing data. We did this by changing missing data to having an event ('worst/best-case' scenario) and then to not having an event ('best/worst-case' scenario) in a sensitivity analysis to investigate the impact of missing data on meta-analysis results.

Assessment of heterogeneity

We described heterogeneity in the data using the Chi^2 test (Deeks 2011). We considered a P value less than 0.05 to be statistically significant heterogeneity (Deeks 2011). We also used the I^2 statistic to measure the quantity of heterogeneity. In case of statistical heterogeneity or clinical heterogeneity (or both), we performed the meta-analysis but interpreted the result cautiously and planned to investigate potential sources to the heterogeneity.

Assessment of reporting biases

We planned to perform and examine a funnel plot to explore possible publication biases. However, as the number of trials included was less than 10, we did not produce any funnel plots (Sterne 2011).

Data synthesis

We performed the meta-analysis using Review Manager 5 (RevMan 2014). For all analyses, we examined both fixed-effect and random-effects models. We reported only the fixed-effect model results when there was no discrepancy between the two models. In case of discrepancy between the two models, we reported both results. We considered a P value less than 0.05 to be statistically significant.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analysis; however, due to too few included trials for each outcome analysis, these were not carried out:

- abdominal surgery versus pelvic surgery;
- elective procedure versus emergency procedure;
- people with high anaesthetic risk (e.g. people with cardiopulmonary disease; American Society of Anesthesiologists (ASA) status III or IV) versus people with low anaesthetic risk (e.g. people without cardiopulmonary disease; ASA status I or II).

Sensitivity analysis

We performed the following sensitivity analyses:

- changing between worst/best-case scenario analysis and best/worst-case scenario analysis for missing data.

If the results did not change, they were considered to be robust.

We also planned to perform the following two sensitivity analyses; however, as all included trials had a high or unclear risk of bias and low numbers of participants, these could not be carried out:

- excluding trials with a high or unclear risk of bias.
- excluding RCTs with small sample sizes.

Trial sequential analysis

We performed trial sequential analysis (TSA) for the primary outcomes if possible. TSA aims to reduce the risk of random error in the setting of repetitive testing of accumulating data, thereby improving the reliability of conclusions (Brok 2008; Wetterslev 2008; Wetterslev 2009). The required information size was calculated on the basis of a risk ratio reduction (RRR) of 20% (Brok 2008; Wetterslev 2008; Wetterslev 2009). The results of the trials were presented as a cumulative Z-curve. The trial sequential monitoring boundaries were constructed and the diversity-adjusted required information size calculated with a type 1 error of 5% and a type 2 error of 20% (Brok 2008; Wetterslev 2008; Wetterslev 2009). TSA was not adjusted for heterogeneity because the estimate of the heterogeneity parameter may be unreliable. The results were presented as a graph with the cumulative meta-analysis results entered. The TSA shows firm evidence of intervention effects (or no intervention effects) if the cumulative Z-curve crosses the monitoring boundaries; it also shows that additional trials may be needed if the boundaries are not crossed (Brok 2008; Wetterslev 2008; Wetterslev 2009). TSA was performed using Trial Sequential Analysis software (TSA 2011).

'Summary of findings' tables

We evaluated the quality of evidence using the GRADE (Schünemann 2009) approach for each outcome, including any subgroup analysis or sensitivity analysis.

We presented the quality of evidence in 'Summary of Finding' tables for the following comparisons:

- nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum;
- helium pneumoperitoneum versus carbon dioxide pneumoperitoneum;
- room air pneumoperitoneum versus carbon dioxide pneumoperitoneum.

Judgements about the quality of the evidence (high, moderate, low, or very low) were justified, documented, and incorporated into the reporting of results for each outcome. The quality of evidence could be downgraded by one level (serious concern) or two levels (very serious concerns) applying to each of the following five reasons listed: risk of bias; inconsistency (unexplained heterogeneity, inconsistency of results); indirectness (indirect population, intervention, control, outcomes); imprecision (wide CIs, single trials); and publication bias.

RESULTS

Description of studies

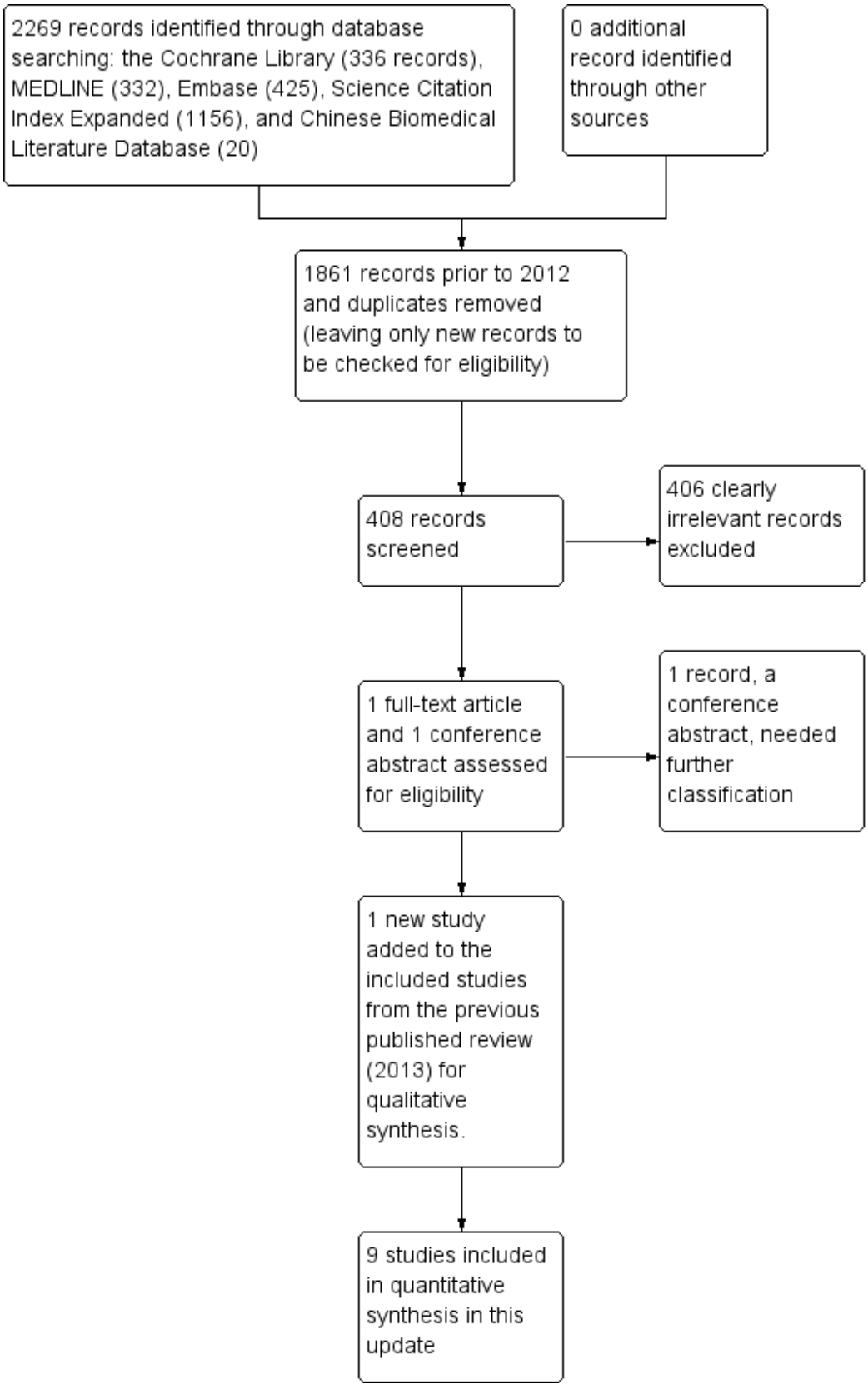
See: Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

In this updated review, we identified 2269 records through the electronic searches of the Cochrane Library (336 records), MEDLINE (Ovid) (332 records), Embase (Ovid) (425 records), Science Citation Index Expanded (Web of Science) (1156 records), and Chinese Biomedical Literature Database (CBM) (20 records). Of the 2269 records, 1861 records had already been assessed for the first version of this updated review (1648 records prior to 2012 and 213 duplicates). Of the remaining 408 records, we excluded 406 clearly irrelevant records through reading titles and abstracts. The remaining two records were retrieved for further assessment (Bergstrom 2015; Gu 2015). The trial by Bergstrom 2015 was a conference abstract. We contacted the original investigators for further information necessary for assessment, but did not receive any feedback. Therefore, this study is awaiting classification. The trial by Sietses 2002, originally excluded in the first published version of this review (Cheng 2013), was re-evaluated and included in this update.

In total, this updated review included nine RCTs. The study flow diagram is shown in Figure 1.

Figure 1. Study flow diagram.



Included studies

In the first published version of this review from 2013, we included seven trials, published between 1993 and 2002 (Aitola 1998; Bongard 1993; Lipscomb 1993; Naude 1996; Neuhaus 2001; O'Boyle 2002; Tsereteli 2002). In this update, we re-evaluated and included the trial by Sietses 2002 and identified one recent trial (Gu 2015), to a total of nine included trials (including 519 participants). Details of the trials are shown in the Characteristics of included studies table. Three trials compared carbon dioxide pneumoperitoneum with nitrous oxide pneumoperitoneum (Aitola 1998; Lipscomb 1993; Tsereteli 2002). Five trials compared carbon dioxide pneumoperitoneum with helium pneumoperitoneum (Bongard 1993; Naude 1996; Neuhaus 2001; O'Boyle 2002; Sietses 2002). One trial compared room (ambient) air pneumoperitoneum with carbon dioxide pneumoperitoneum (Gu 2015). Studies were conducted in the USA (Bongard 1993; Lipscomb 1993; Naude 1996; Tsereteli 2002), Australia (Neuhaus 2001; O'Boyle 2002), China (Gu 2015), Finland (Aitola 1998), and Netherlands (Sietses 2002). The age of the participants varied between 19 and 62 years. The proportion of women varied between 45.5% and 100%. Participants underwent various elective laparoscopic general abdominal or gynaecological pelvic procedures (e.g. cholecystectomy, fundoplication (anti-reflux surgery), hernia repair, tubal ligation). The outcomes measured were complications, pneumoperitoneum-related serious adverse events, cardiopulmonary changes, pain scores, hospital costs, and mortality.

Excluded studies

We excluded seven studies. One RCT included participants who underwent laparoscopic pelvic surgery performed by gynaecological surgeons under local anaesthesia (Lipscomb 1994). Another RCT focused on diagnostic laparoscopy performed under local anaesthesia (Sharp 1982). None of the other excluded studies were RCTs (Fernández-Cruz 1998; McMahon 1994; Neuberger 1996; Ooka 1993; Rammohan 2011).

Ongoing studies

We identified one ongoing study. Sixty-four participants (all with low anaesthetic risk) undergoing laparoscopic cholecystectomy will be randomised to nitrous oxide pneumoperitoneum or carbon dioxide pneumoperitoneum (Asgari 2012). This trial is currently recruiting participants, being performed in Iran, and was initiated November 2010. The primary outcome is heart rate. The secondary outcome is mean arterial pressure (see Characteristics of ongoing studies table).

Risk of bias in included studies

The risk of bias of the included studies is shown in Figure 2 and Figure 3. None of the included trials was at low risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

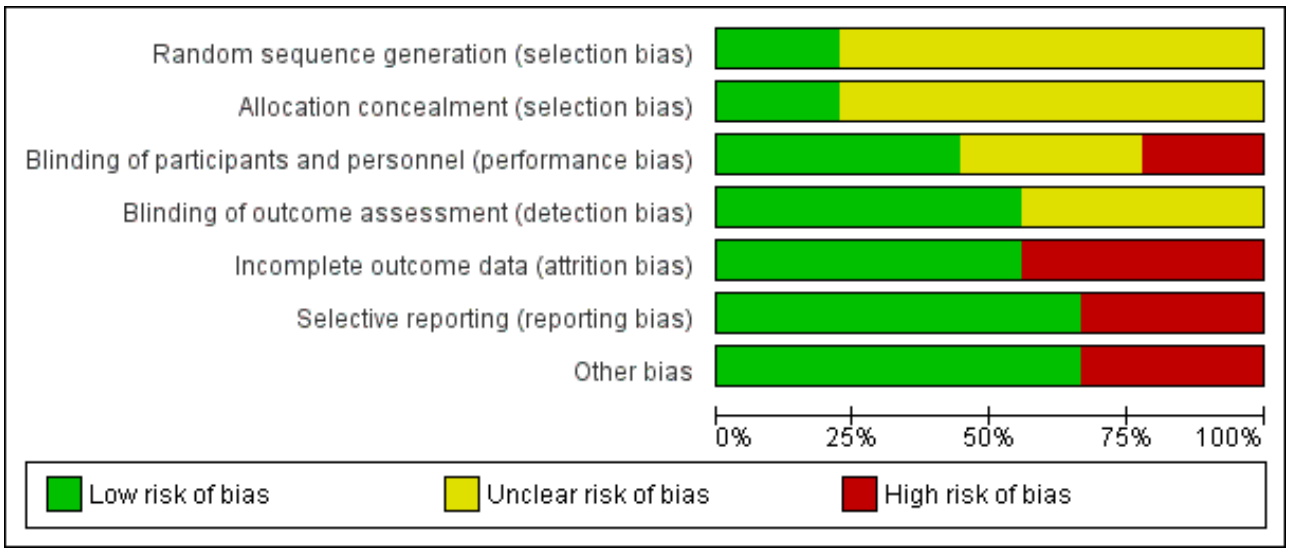
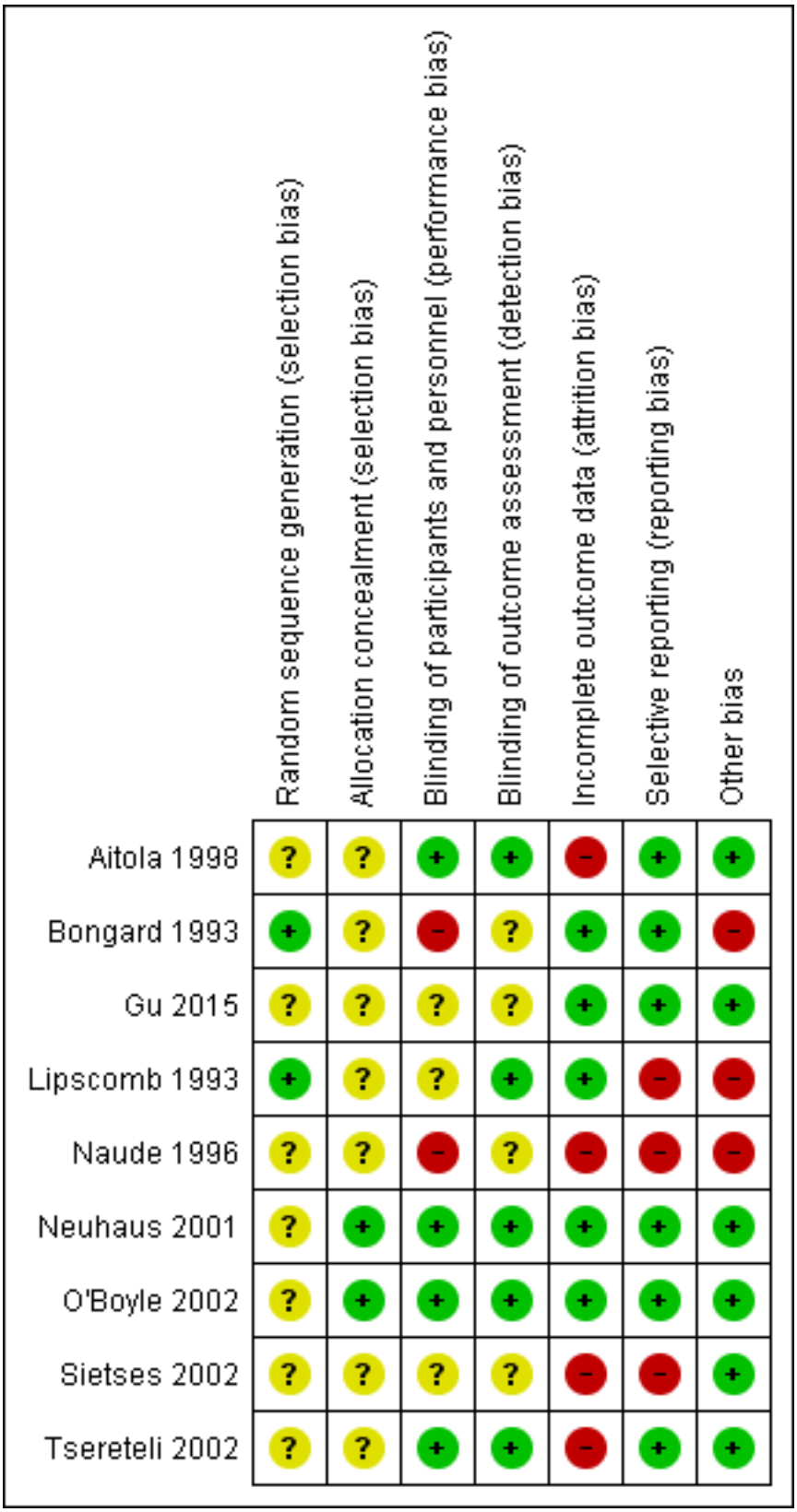


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation was at low risk of bias in two trials where participants were randomised using computer-generated numbers (Bongard 1993; Lipscomb 1993), and unclear risk of bias in seven trials (Aitola 1998; Gu 2015; Naude 1996; Neuhaus 2001; O'Boyle 2002; Sietses 2002; Tsereteli 2002). Allocation concealment was at low risk of bias in two trials that used sealed opaque envelopes to conceal the allocations (Neuhaus 2001; O'Boyle 2002), and unclear risk of bias in the remaining seven studies (Aitola 1998; Bongard 1993; Gu 2015; Lipscomb 1993; Naude 1996; Sietses 2002; Tsereteli 2002).

Blinding

Blinding of participants and personnel was at low risk of bias in four trials (Aitola 1998; Neuhaus 2001; O'Boyle 2002; Tsereteli 2002), unclear risk of bias in three trials (Gu 2015; Lipscomb 1993; Sietses 2002), and high risk of bias in two trials (Bongard 1993; Naude 1996). Blinding of outcome assessment was at low risk of bias in five trials (Aitola 1998; Lipscomb 1993; Neuhaus 2001; O'Boyle 2002; Tsereteli 2002), and unclear risk of bias in four trials (Bongard 1993; Gu 2015; Naude 1996; Sietses 2002).

Incomplete outcome data

There were no postrandomisation dropouts in three trials (Gu 2015; Lipscomb 1993; Neuhaus 2001). Although there were seven dropouts (6.4%) in two trials, the data were analysed on an intention-to-treat basis (Bongard 1993; O'Boyle 2002). These five trials were considered at low risk of attrition bias. There were 12 dropouts (6.2%) in the other four trials (Aitola 1998; Naude 1996; Sietses 2002; Tsereteli 2002), but the data were not analysed on an intention-to-treat basis. Thus, these four trials were at high risk of attrition bias. The reasons for the dropouts were reported in the Characteristics of included studies table.

Selective reporting

The trial protocols were not available for any of the trials. Six trials reported all of the important pneumoperitoneum-related outcomes (primary outcomes of this review) (Aitola 1998; Bongard 1993; Gu 2015; Neuhaus 2001; O'Boyle 2002; Tsereteli 2002). There may have been selective outcome reporting in the secondary outcomes, but the review authors considered these six trials to be free of selective reporting for the primary outcomes of the review. Three trials were at high risk of selective reporting bias as none of the primary outcomes of the review were reported (Lipscomb 1993; Naude 1996; Sietses 2002).

Other potential sources of bias

Three trials presented considerable baseline imbalance, thus we considered these at high risk of bias (Bongard 1993; Lipscomb 1993; Naude 1996).

Effects of interventions

See: **Summary of findings for the main comparison** Nitrous oxide versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery; **Summary of findings 2** Helium versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery; **Summary of findings 3** Room air versus carbon dioxide for establishing pneumoperitoneum during laparoscopic abdominal surgery

1. Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum

Three trials with 196 participants compared nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (Aitola 1998; Lipscomb 1993; Tsereteli 2002). See Summary of findings for the main comparison.

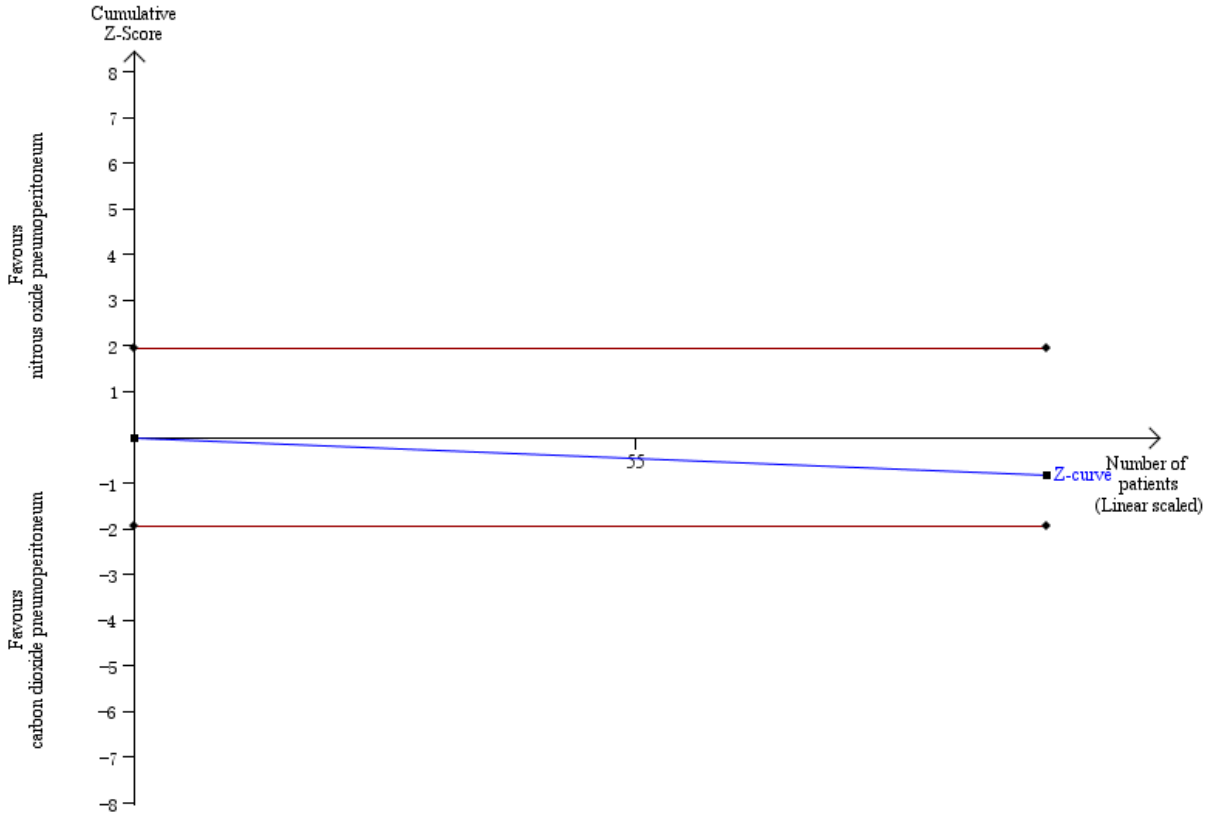
1.1. Primary outcomes

1.1.1. Cardiopulmonary complications (Analysis 1.1)

Two trials (140 participants) reported cardiopulmonary complications (Aitola 1998; Tsereteli 2002). The cardiopulmonary complication rate was 5.7% in the nitrous oxide group and 2.9% in the carbon dioxide group. There was no evidence of a difference in cardiopulmonary complications between the groups (RR 2.00, 95% CI 0.38 to 10.43; low-quality evidence; Analysis 1.1). There was clinical heterogeneity because the two trials performed quite different laparoscopic operations (cholecystectomy versus foregut surgery). This finding was downgraded to very low quality due to very serious study limitations (incomplete outcome data and selective reporting) and serious imprecision (wide CIs and small sample size).

The TSA graph showed that the cumulative Z-curve did not cross the naive 5% statistical boundaries (Figure 4). The analysis showed a diversity-adjusted required information size of 3781 participants (the number of participants needed to reach firm evidence of an intervention effect of 20% RRR). The number of participants included corresponded to only a small fraction (3.7%) of the diversity-adjusted required information size; therefore, the trial sequential boundaries could not be drawn. Accordingly, we lack evidence to conclude equivalence of nitrous oxide and carbon dioxide pneumoperitoneum.

Figure 4. Trial sequential analysis of nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum for cardiopulmonary complications. Analysis was performed with an event rate of 2.9% (Pc) in the control group, a risk ratio reduction of 20%, alpha 5%, beta 20%, and observed diversity 0%. The accrued sample size was so small that the trial sequential boundaries could not be drawn. The cumulative Z-curve did not cross the naive 5% statistical boundaries (red horizontal lines). The results showed that the observed diversity-adjusted required information size was 3781 participants, corresponding to 3.7% of the total sample size in the included trials. Accordingly, the meta-analysis did not support or refute an intervention effect as data were too few.

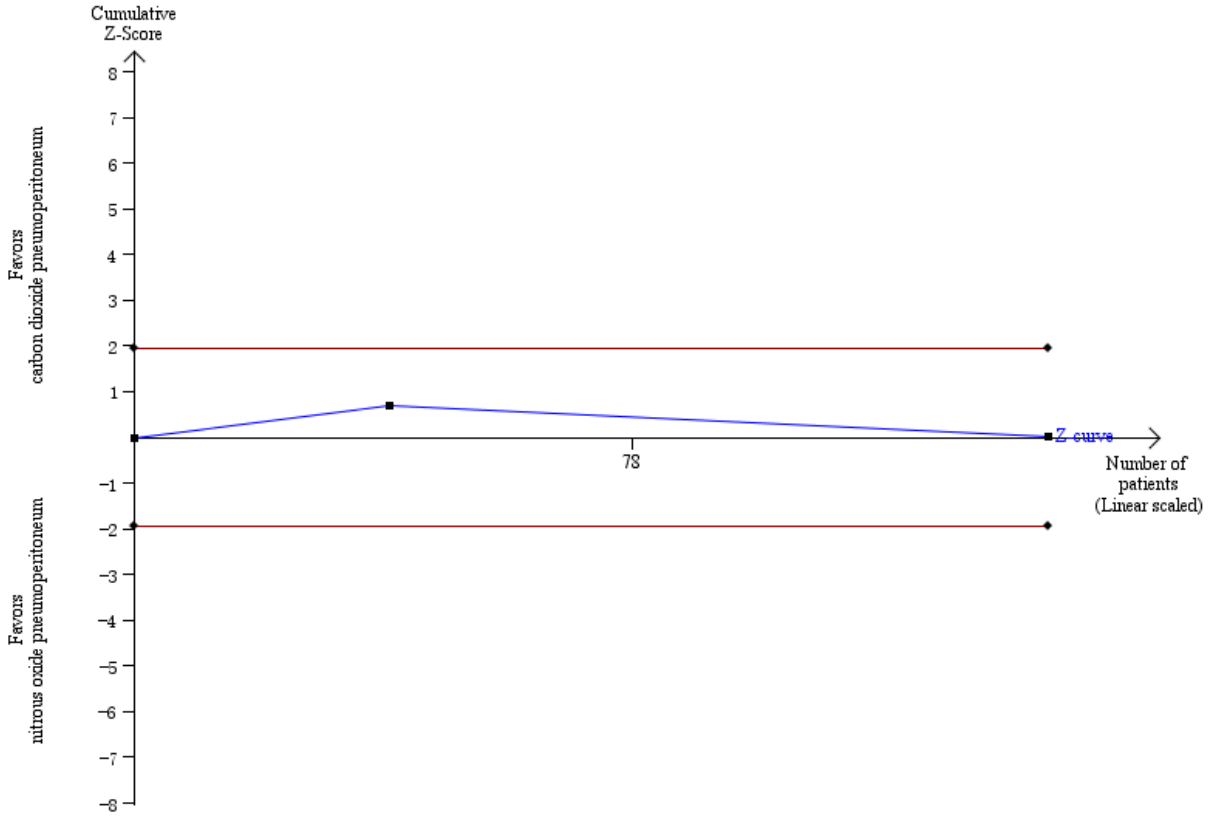


1.1.2. Procedure-related general complications (surgical morbidity) (Analysis 1.2)

Two trials (143 participants) reported surgical morbidity (Aitola 1998; Tsereteli 2002). The surgical morbidity was 2.8% in the nitrous oxide group versus 2.8% in the carbon dioxide group. There was no evidence of a difference in the surgical morbidity (procedure-related general complications) between the groups (RR 1.01, 95% 0.18 to 5.71; very-low-quality evidence; Analysis 1.2). There was clinical heterogeneity because the two trials performed quite different laparoscopic operations (cholecystectomy versus foregut surgery). This finding was downgraded to very low quality due to very serious study limitations (incomplete outcome data and selective reporting) and serious imprecision (wide CIs and small sample size).

The TSA graph showed that the cumulative Z-curve did not cross the naive 5% statistical boundaries (Figure 5). The analysis showed a required information size of 3919 participants (the number of participants needed to reach firm evidence of an intervention effect of 20% RRR). The number of participants included corresponded to only a small fraction (3.6%) of the diversity-adjusted required information size; therefore, the trial sequential boundaries could not be drawn. Accordingly, we lack evidence to conclude equivalence of nitrous oxide and carbon dioxide pneumoperitoneum.

Figure 5. Trial sequential analysis of nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum for surgical morbidity. Analysis was performed with an event rate of 2.8% (Pc) in the control group, a risk ratio reduction of 20%, alpha 5%, beta 20%, and observed diversity 0%. The cumulative Z-curve did not cross the naive 5% statistical boundaries (red horizontal lines). The results showed that the observed diversity adjusted required information size was 3919 participants, corresponding to 3.6% of the total sample size in the included trials. Accordingly, the meta-analysis did not support or refute an intervention effect as data were too few.



1.1.3. Pneumoperitoneum-related serious adverse events

None of the trials reported any pneumoperitoneum-related serious adverse events. This finding was downgraded to low quality of evidence due to serious study limitations (incomplete outcome data) and serious imprecision (small sample size for such a rare outcome).

1.2. Secondary outcomes

1.2.1. Mortality

None of the trials reported any deaths. This finding was downgraded to low quality of evidence due to serious study limitations (incomplete outcome data) and serious imprecision (small sample size for such a rare outcome).

1.2.2. Quality of life

None of the trials reported quality of life.

1.2.3. Pain scores

Two trials (140 participants) reported pain scores (Aitola 1998; Tsereteli 2002). Both reported lower pain scores (about 1 cm on a VAS scale of 1 cm to 10 cm with lower numbers indicating less pain) in the nitrous oxide group compared with the carbon dioxide group at various time points on the first postoperative day. However, as neither trial reported the standard deviation (SD) for pain scores, we did not perform a meta-analysis. There was clinical heterogeneity because the trials performed quite different laparoscopic operations (cholecystectomy versus foregut surgery). This finding was downgraded to very low quality of evidence due to study limitations (incomplete outcome data), indirectness and serious imprecision (small sample size).

Another trial reported pain scores using McGill pain questionnaire, but was not considered for this outcome, because it did not use the VAS scale (Lipscomb 1993, 53 participants undergoing laparoscopic tubal ligation).

1.2.4. Analgesia requirements (Analysis 1.3)

Three trials (193 participants) reported analgesia requirements. The trials used different measurement scales (milligrams versus tablets per 24 hours), therefore we calculated a SMD. The fixed-effect model showed less analgesic consumption (oxycodone or

ibuprofen) in the nitrous oxide group compared with the carbon dioxide group (SMD -0.79, 95% CI -1.09 to -0.49; very low quality evidence). The statistical heterogeneity was substantial (I^2 = 82%) and applying the random-effects model did not show any evidence of difference in analgesic consumption between the groups (SMD -0.69, 95% CI -1.42 to 0.04; very-low-quality evidence; Analysis 1.3). In addition, there was clinical heterogeneity because the three trials performed quite different laparoscopic operations (cholecystectomy, foregut surgery, tubal ligation). Consequently, this finding was downgraded to very low quality of evidence due to study limitations (incomplete outcome data), serious imprecision (small sample size), and serious inconsistency.

1.2.5. Costs

None of the trials reported costs.

1.2.6. Cardiopulmonary changes (Analysis 1.4)

One trial (100 participants) reported cardiopulmonary changes (Tsereteli 2002). There was no evidence of a difference in the following cardiopulmonary parameter changes between the groups: heart rate (MD -0.60 beats/minute, 95% CI -4.13 to 2.93; very-low-quality evidence), mean arterial pressure (MD -3.80 mmHg, 95% CI -7.90 to 0.30; very-low-quality evidence), oxygen saturation (MD 0%, 95% CI -0.39 to 0.39; very low quality of evidence), and peak airway pressure (MD -0.30 cmH_2O, 95% CI -2.17 to 1.57; very low quality of evidence) (Analysis 1.4). None of the other cardiopulmonary changes were reported. These findings were downgraded to very low quality of evidence due to study limitations (incomplete outcome data), serious imprecision (small sample size), and indirectness of the outcome (surrogate outcome).

2. Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum

Five trials (177 participants) reported helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (Bongard 1993; Naude 1996; Neuhaus 2001; O'Boyle 2002; Sietses 2002). See Summary of findings 2.

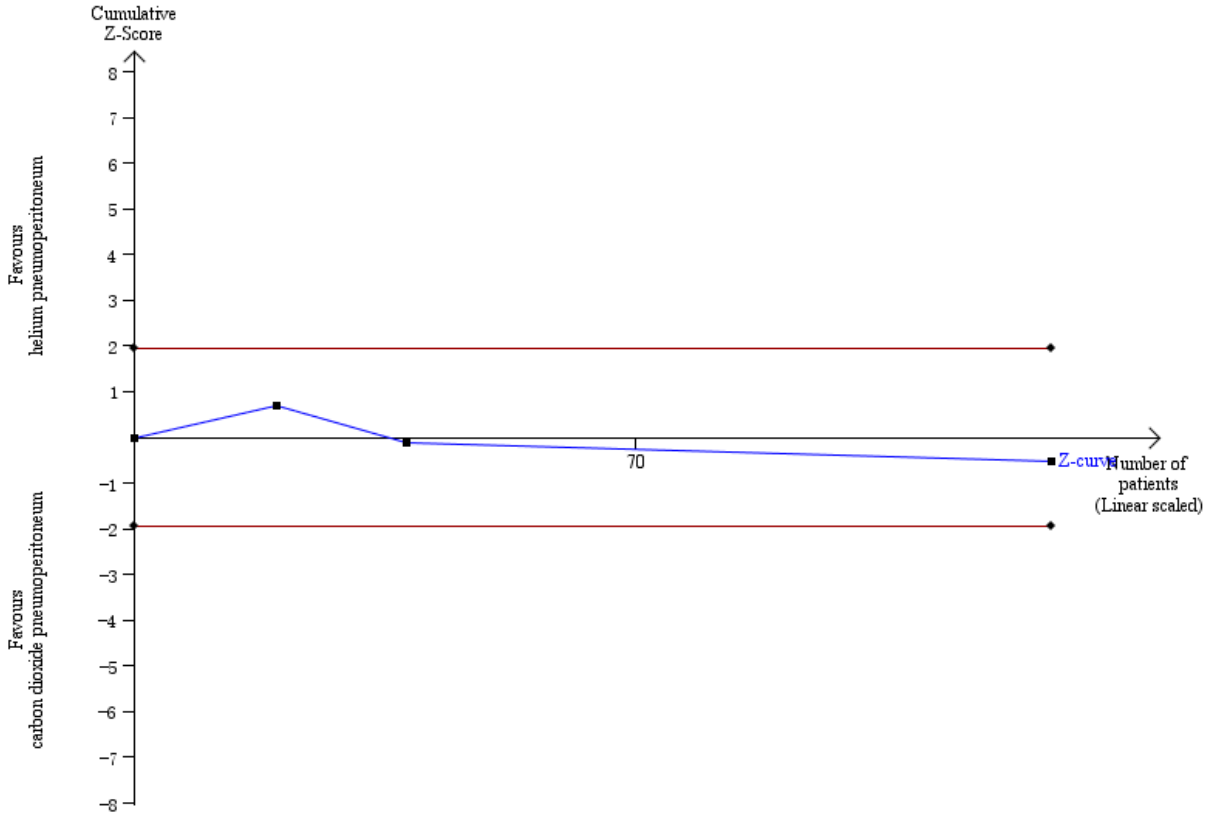
2.1. Primary outcomes

2.1.1. Cardiopulmonary complications (Analysis 2.1)

Three trials (128 participants) reported cardiopulmonary complications (Bongard 1993; Neuhaus 2001; O'Boyle 2002). The cardiopulmonary complication rate was 4.4% in the helium group and 3.0% in the carbon dioxide group. There was no evidence of a difference in cardiopulmonary complications between the groups (RR 1.46, 95% CI 0.35 to 6.12; very-low-quality evidence; Analysis 2.1). There was clinical heterogeneity because the three trials performed quite different laparoscopic operations (e.g. cholecystectomy, fundoplication, and gastrointestinal surgery). This finding was downgraded to very low quality of evidence due to serious study limitations (lack of blinding and selective reporting) and very serious imprecision (wide CIs and small sample size).

The TSA graph showed that the cumulative Z-curve did not cross the naive 5% statistical boundaries (Figure 6). The analysis showed a diversity-adjusted required information size of 3651 participants (the number of participants needed to reach firm evidence of an intervention effect of 20% RRR). The number of participants included corresponded to only a small fraction (3.5%) of the diversity-adjusted required information size; therefore, the trial sequential boundaries could not be drawn. Accordingly, we lack evidence to conclude equivalence of helium and carbon dioxide pneumoperitoneum.

Figure 6. Trial sequential analysis of helium pneumoperitoneum versus carbon dioxide pneumoperitoneum for cardiopulmonary complications. Analysis was performed with an event rate of 3.0% (Pc) in the control group, a risk ratio reduction of 20%, alpha 5%, beta 20%, and observed diversity 0%. The cumulative Z-curve did not cross the naive 5% statistical boundaries (red horizontal lines). The results showed that the observed diversity adjusted required information size was 3651 participants, corresponding to 3.5% of the total sample size in the included trials. Accordingly, the meta-analysis did not support or refute an intervention effect as data were too few.



2.1.2. Procedure-related general complications (surgical morbidity)

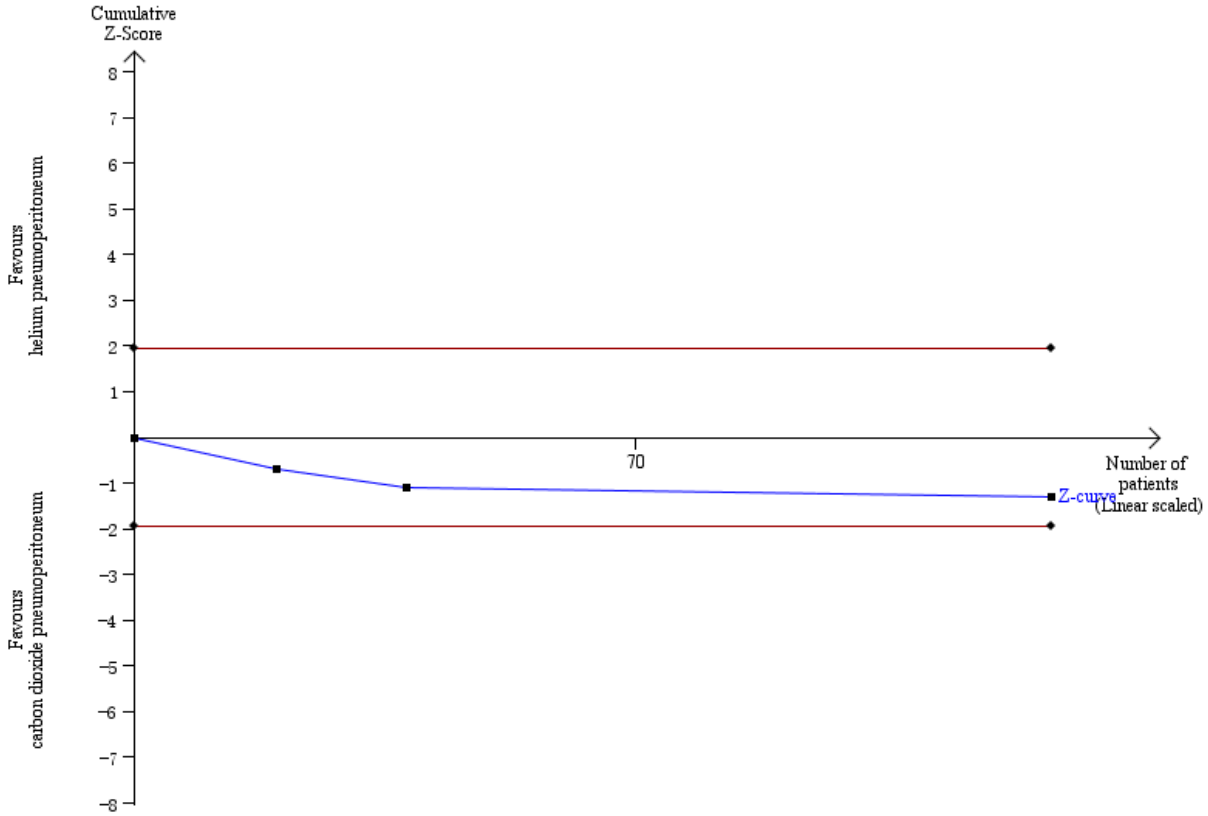
None of the trials reported any significant procedure-related general complications. This finding was downgraded to very low quality of evidence due to very serious study limitations (lack of blinding, incomplete outcome data, and other bias) and serious imprecision (small sample size).

2.1.3. Pneumoperitoneum-related serious adverse events (Analysis 2.2)

Three trials (128 participants) reported serious adverse events (Bongard 1993; Neuhaus 2001; O'Boyle 2002). There were three serious adverse events (subcutaneous emphysema) related to helium pneumoperitoneum; the serious adverse event rate was 4.9% in the helium pneumoperitoneum group and 0% in the carbon dioxide pneumoperitoneum group. There was no evidence of a difference in the Peto OR for pneumoperitoneum-related serious adverse events between groups (Peto OR 8.28, 95% CI 0.86 to 80.03; very low quality of evidence; Analysis 2.2). There was clinical heterogeneity because the three trials performed quite different laparoscopic operations. This finding was downgraded to very low quality evidence due to study limitations (lack of blinding and selective reporting), indirectness and serious imprecision (small sample size for such a rare outcome).

The TSA graph showed that the cumulative Z-curve did not cross the naive 5% statistical boundaries (Figure 7). The analysis showed a diversity-adjusted required information size of 4793 participants (the number of participants needed to reach firm evidence of an intervention effect of 20% RRR). The number of participants included corresponded to only 2.7% of the diversity-adjusted required information size; therefore, the trial sequential boundaries could not be drawn. Accordingly, we lack evidence to conclude equivalence of helium and carbon dioxide pneumoperitoneum.

Figure 7. Trial sequential analysis of helium pneumoperitoneum versus carbon dioxide pneumoperitoneum for serious adverse events. Analysis was performed with an event rate of 2.3% (Pc) in the control group, a risk ratio reduction of 20%, alpha 5%, beta 20%, and observed diversity 0%. The cumulative Z-curve did not cross the naive 5% statistical boundaries (red horizontal lines). The results showed that the observed diversity adjusted required information size was 4793 participants, corresponding to 2.7% of the total sample size in the included trials. Accordingly, the meta-analysis did not support or refute an intervention effect as data were too few.



2.2. Secondary outcomes

2.2.1. Mortality

None of the trials reported any deaths. This finding was downgraded to low quality of evidence due to serious risk of bias and imprecision (small sample size for such a rare outcome).

2.2.2. Quality of life

None of the trials reported quality of life.

2.2.3. Pain scores (shoulder or abdominal pain) (Analysis 2.3)

Two trials (108 participants) reported pain scores (Neuhaus 2001; O'Boyle 2002). There was no evidence of a difference in the first postoperative day pain scores (graded by VAS on a scale of 1 cm to 10 cm, with lower numbers indicating less pain) between the groups (MD 0.49 cm, 95% CI -0.28 to 1.26; very low quality evidence; Analysis 2.3). There was clinical heterogeneity because the two trials performed quite different laparoscopic operations. This finding was downgraded to very low quality of evidence due to study limitations (random sequence generation was at unclear risk), indirectness and serious imprecision (small sample size).

2.2.4. Analgesia requirements (Analysis 2.4; Analysis 2.5)

Two trials (108 participants) reported analgesia requirements (Neuhaus 2001; O'Boyle 2002). One trial reported the amount of analgesia consumed (O'Boyle 2002). The overall analgesic (morphine) consumption was higher in the helium group than the carbon dioxide group (MD 12.00 mg, 95% CI 4.44 to 19.56; very-low-quality evidence; Analysis 2.4). One trial reported the number of participants requiring analgesia (Neuhaus 2001). There was no evidence of a difference in analgesia (morphine) requirements between the helium group (3/8; 37.5%) and carbon dioxide group (9/10; 90%) (Analysis 2.5). However, the trial was underpowered with only 18 participants (very low quality of evidence). There was clinical heterogeneity because the two trials performed quite different laparoscopic operations. This finding was downgraded to very low quality of evidence due to study limitations (random sequence generation was at unclear risk), indirectness and serious imprecision (small sample size).

2.2.5. Costs

None of the trials reported costs.

2.2.6. Cardiopulmonary changes (Analysis 2.6)

Two trials (34 participants) reported blood pH (Bongard 1993; Naude 1996). There was no evidence of a differences between the groups in blood pH at the start of pneumoperitoneum (MD 0.01, 95% CI -0.01 to 0.04; very-low-quality evidence) or the middle of pneumoperitoneum (MD -0, 95% CI -0.03 to 0.02; very-low-quality evidence). However, the blood pH was higher in the helium group compared with the carbon dioxide group at the end of pneumoperitoneum (MD 0.10, 95% CI -0.06 to -0.14; very-low-quality evidence). Three trials (52 participants) reported partial pressure of carbon dioxide (Bongard 1993; Naude 1996; Neuhaus 2001). There was no evidence of differences between the groups in partial pressure of carbon dioxide at the start of pneumoperitoneum (MD 0.31 mmHg, 95% CI -1.79 to 2.40; very-low-quality evidence) or the middle of pneumoperitoneum (MD 0.84 mmHg, 95% CI -2.02 to 3.70; very-low-quality evidence). However, the partial pressure of carbon dioxide was lower in the helium group than the carbon dioxide group at the end of pneumoperitoneum (MD -12.78 mmHg, 95% CI -16.78 to -8.77; very-low-quality evidence). There was clinical heterogeneity because the included trials performed quite different laparoscopic operations. These findings were downgraded to very low quality of evidence due to study limitations (lack of blinding, incomplete outcome data, and other bias), serious imprecision (small sample size), and indirectness of the outcome (surrogate outcome).

3. Room (ambient) air pneumoperitoneum versus carbon dioxide pneumoperitoneum

Only one trial (146 participants) reported room (ambient) air pneumoperitoneum versus carbon dioxide pneumoperitoneum (Gu 2015). See Summary of findings 3.

3.1. Primary outcomes

3.1.1. Cardiopulmonary complications

The trial did not report any cardiopulmonary complications. This finding was downgraded to very low quality of evidence due to very serious study limitations (allocation and blinding were unclear) and serious imprecision (small sample size).

3.1.2. Procedure-related general complications (surgical morbidity)

The trial did not report surgical morbidity.

3.1.3. Pneumoperitoneum-related serious adverse events

The trial did not report any pneumoperitoneum-related serious adverse events. This finding was downgraded to very low quality of evidence due to very serious study limitations (allocation and blinding were unclear) and serious imprecision (small sample size for such a rare outcome).

3.2. Secondary outcomes

3.2.1. Mortality

The trial did not report any deaths. This finding was downgraded to low quality of evidence due to study limitations (allocation and blinding were unclear) and serious imprecision (small sample size for such a rare outcome).

3.2.2. Quality of life

The trial did not report quality of life.

3.2.3. Pain scores (Analysis 3.3)

The first postoperative day pain scores (graded by VAS on a scale of 1 cm to 10 cm with lower numbers indicating less pain) were lower in the room air group than in the carbon dioxide group (MD -0.80 cm, 95% CI -1.15 to -0.45; very low quality evidence). This finding was downgraded to very low quality of evidence due to very serious study limitations (allocation and blinding were unclear) and serious imprecision (small sample size).

3.2.4. Analgesia requirements

The trial did not report analgesia requirements.

3.2.5. Costs (Analysis 3.4)

The total hospital costs were lower in the room air group than in the carbon dioxide group (MD -CNY2667.00, 95% CI -3275.68 to -2058.32; very-low-quality evidence; equivalent to approximately USD300 to USD475 in November 2016). This finding was downgraded to very low quality of evidence due to very serious study limitations (allocation and blinding were unclear) and serious imprecision (small sample size).

3.2.6. Cardiopulmonary changes (Analysis 3.5)

There was no evidence of a difference between groups in heart rate at the start of pneumoperitoneum (MD -0.10 beats/minute, 95% CI -3.11 to 2.91; very-low-quality evidence). However, heart rate was lower in the room air group compared with the carbon dioxide group in the middle of pneumoperitoneum (MD -7.30 beats/minute, 95% CI -9.78 to -4.82; very low quality evidence) and the end of pneumoperitoneum (MD -8.70 beats/minutes, 95% CI -11.72 to -5.68; very low quality evidence) of pneumoperitoneum (Analysis 3.5).

There was no evidence of differences between groups in blood systolic pressure or partial pressure of carbon dioxide at the start, middle, or end of pneumoperitoneum (all very low quality evidence).

All these findings were downgraded to very low quality of evidence due to study limitations (allocation and blinding were unclear), serious imprecision (small sample size), and indirectness of the outcome (surrogate outcome).

4. Reporting bias

We did not perform funnel plots to assess reporting biases because the number of included trials was less than 10. We did not identify any study protocols or trials registration records. Three trials were regarded as high risk of reporting bias as none of the trials did not investigate the primary outcomes (Lipscomb 1993; Naude 1996; Sietses 2002).

5. Subgroup analysis

None of the planned subgroup analyses was performed due to the limited number of included trials for each outcome.

6. Sensitivity analysis

We performed worst/best-case scenario and best/worst-case scenario analyses for the outcomes cardiopulmonary complications, procedure-related general complications (surgical morbidity), pneumoperitoneum-related serious adverse events, and mortality to assess the impact of missing data for 13

postrandomisation dropouts across five trials (Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 5.4; Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 7.1; Analysis 7.2; Analysis 7.3; Analysis 7.4). Results are presented in Table 1. Assigning death or no death to all missing participants in the helium versus carbon dioxide pneumoperitoneum comparison altered the conclusion drawn, confirming that the low mortality rate and small numbers of participants were insufficient to reliably assess this outcome. The other three outcomes (cardiopulmonary complications, procedure-related general complications, and pneumoperitoneum-related serious adverse events) also changed by assigning event or no event to all missing participants in the helium versus carbon dioxide pneumoperitoneum comparison.

DISCUSSION

Summary of main results

Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum

Three studies with 196 people contributed data to the primary outcomes of this review, and showed no evidence of differences between nitrous oxide pneumoperitoneum and carbon dioxide pneumoperitoneum in any of the primary outcomes, such as cardiopulmonary complications or surgical morbidity. There were no serious adverse events related to the use of nitrous oxide or carbon dioxide pneumoperitoneum. Two trials showed lower pain scores (a difference of about 1 cm on a VAS scale of 1 cm to 10 cm with lower numbers indicating less pain) in nitrous oxide pneumoperitoneum at various time points on the first postoperative day. However, we do not consider 1 cm on a VAS scale to be clinically significant - as this difference is less than the minimum important clinical difference (Katz 2015; Parker 2013; Todd 1996).

The safety of nitrous oxide pneumoperitoneum is another major concern for patients, laparoscopic surgeons, and healthcare funders. Exposure to nitrous oxide may be harmful to laparoscopic surgeons because nitrous oxide has an anaesthetic effect. This review included three trials with 100 participants undergoing nitrous oxide pneumoperitoneum. Although none of the trials reported any serious adverse events in the nitrous oxide group, they did not have the statistical power to establish the safety of nitrous oxide pneumoperitoneum. The TSA showed an information size of more than 3700 participants is needed to reach firm evidence for primary outcomes. As this review included only three trials with 196 participants for this comparison, there is lack of evidence to support or refute the effectiveness or safety of nitrous oxide pneumoperitoneum compared with carbon dioxide pneumoperitoneum.

Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum

Four studies with 144 people contributed data to the primary outcomes of this review, and showed no evidence of differences between helium pneumoperitoneum and carbon dioxide pneumoperitoneum in any of the primary outcomes, such as cardiopulmonary complications or surgical morbidity. There were three serious adverse events related to helium pneumoperitoneum. Although there were fewer cardiopulmonary changes in the helium pneumoperitoneum group, this did not translate into any clinical benefit.

In contrast to other gases used for creating a pneumoperitoneum, helium is an inert gas that has extremely low reactivity with other substances. The safety of helium pneumoperitoneum is also an important outcome for patients, laparoscopic surgeons, and healthcare funders. This review included four trials with 69 participants undergoing helium pneumoperitoneum. Three of the four trials reported a total of three serious adverse events related to pneumoperitoneum in the helium group. The adverse events were various subcutaneous emphysemas (e.g. scrotal, facial, and cervical emphysema). Although the meta-analysis did not demonstrate any evidence of differences in pneumoperitoneum-related serious adverse events between helium and carbon dioxide pneumoperitoneum, it also did not have the statistical power to establish the safety of helium pneumoperitoneum. The TSA showed an information size of more than 3600 participants needed to reach firm evidence for primary outcomes. As this review included only four trials with 144 participants in this comparison, there is lack of evidence to support or refute the effectiveness or safety of helium pneumoperitoneum compared with carbon dioxide pneumoperitoneum.

Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum

One study with 146 people contributed data to the primary outcomes of this review, and showed no evidence of differences between room air pneumoperitoneum and carbon dioxide pneumoperitoneum in cardiopulmonary complications. There were no serious adverse events related to either room air or carbon dioxide pneumoperitoneum. The benefits for room air pneumoperitoneum were fewer total hospital costs (about USD380).

Hospital cost is an important outcome for healthcare funders. The trial showed decreased total hospital costs in the room air group; this could be due to a shorter duration of hospitalisation in the room air group (2.5 days) than in the carbon dioxide group (3.2 days), less analgesic consumption in the room air group, or both. In addition, the cost of carbon dioxide cylinders and carbon dioxide insufflators may be higher than the cost of room air insufflators.

The safety of room air pneumoperitoneum is another major concern for patients, laparoscopic surgeons, and healthcare funders because of the risk of air embolism (Ikechebelu 2005). This review included one trial with 70 participants undergoing room air pneumoperitoneum. Although the trial did not report any serious adverse events in the room air group, it did not have the statistical power to establish the safety of room air pneumoperitoneum. Accordingly, there is lack evidence to support or refute the effectiveness or safety of room air pneumoperitoneum compared with carbon dioxide pneumoperitoneum.

Overall completeness and applicability of evidence

Only 24 participants in two trials (12.6%) had high anaesthetic risk (ASA III or IV) (O'Boyle 2002; Tsereteli 2002). Of the remaining trials, three trials excluded participants with ASA III or IV (Aitola 1998; Bongard 1993; Sietses 2002); and four trials did not report ASA status (Gu 2015; Lipscomb 1993; Naude 1996; Neuhaus 2001). Thus, the results of this review are primarily applicable in ASA I or ASA II patients undergoing various laparoscopic abdominal surgeries

under general anaesthesia. However, this review involved only 519 participants and lacked sufficient power to support or refute any gas for establishing pneumoperitoneum. Thus, further trials on this topic are urgently needed.

Quality of the evidence

Overall, the quality of the evidence was very low for the outcomes for which we could assess the quality of evidence (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).The major reason for downgrading the quality of evidence was serious or very serious risk of bias in the trials. One of the major sources of bias was lack of blinding. Lack of blinding might introduce detection bias and performance bias. Blinding of healthcare providers, participants, and outcome assessors can be achieved with appropriate study design. Another major source of bias was incomplete outcome data. A total of 13/269 (4.8%) participants were excluded from the analysis for various reasons in five trials (Aitola 1998; Bongard 1993; Naude 1996; O'Boyle 2002; Tsereteli 2002). Only two trials analysed the data on an intention-to-treat basis (Bongard 1993; O'Boyle 2002). In addition, sensitivity analysis by changing between worst-case scenario analysis and best-case scenario analysis for missing data revealed that some results changed in the helium pneumoperitoneum versus carbon dioxide pneumoperitoneum comparison. The third major source of bias was selective reporting (reporting bias) as not all trials reported the primary outcomes.

We further downgraded the quality of evidence due to indirectness of the outcomes in trials (e.g. surrogate outcomes such as cardiopulmonary changes). We also downgraded the quality of evidence due to imprecision; the review included only 519 participants in total, with the actual number included in specific outcomes being less than this since not all studies reported all the outcomes in each comparison. There was also clinical heterogeneity among the included trials. As a result of these factors, the confidence intervals for the majority of outcomes were wide, indicating that the estimates of effects obtained were based on an insufficient amount of information, reducing the quality of the evidence. The trials included under each comparison were too few to assess publication bias.

Potential biases in the review process

There were several unavoidable potential biases of note in the review process.

First, this review involved only 519 participants and therefore, was too underpowered to detect differences reliably for the rarer outcomes, such as serious adverse events (e.g. gas embolism, abdominal explosion).

Second, when we contacted the original investigators to request further information, there was no reply. Additionally, we were unable to explore publication bias because of the few trials included in each comparison.

Agreements and disagreements with other studies or reviews

The systematic review (a clinical practice guideline) by Neudecker and colleagues (Neudecker 2002) included two trials (Aitola 1998; Bongard 1993), which were included in this review. Neudecker and colleagues concluded that using insufflation gases such as nitrous oxide, helium, or argon appears to reduce pain, but they did not feel that this justified a general recommendation for the use of these gases. Our review agrees with their conclusion on nitrous oxide pneumoperitoneum, that the effectiveness or safety (or both) of nitrous oxide pneumoperitoneum have not been established. However, our review did not observe a reduction in pain with helium pneumoperitoneum. Furthermore, the authors of two trials comparing nitrous oxide pneumoperitoneum with carbon dioxide pneumoperitoneum (Aitola 1998; Tsereteli 2002) recommended nitrous oxide pneumoperitoneum for prolonged laparoscopic surgery in people with chronic cardiopulmonary diseases; our review did not agree with the conclusions of the trial authors. Due to the lack of evidence, we conclude that further assessment for ASA III or ASA IV patients is required.

AUTHORS' CONCLUSIONS

Implications for practice

The effects of nitrous oxide and helium pneumoperitoneum when compared with carbon dioxide pneumoperitoneum are uncertain. Evidence from one trial of small sample size suggests that room air pneumoperitoneum may decrease hospital costs in people undergoing laparoscopic abdominal surgery. The quality of the current evidence is very low. The safety of nitrous oxide, helium, and room air pneumoperitoneum has yet to be established.

Implications for research

Further trials with sufficient sample size are needed to compare various gases (e.g. nitrous oxide, helium, argon, nitrogen, room air) with carbon dioxide under standard pressure pneumoperitoneum with cold gas insufflation for people with high anaesthetic risk. Future trials should include outcomes such as complications, serious adverse events, quality of life, and pain. There is a lack of data for low-income settings. It is important to work out if cheaper and more available gases than carbon dioxide can be used to facilitate laparoscopic abdominal surgery. Further randomised controlled trials performed in low-income countries are necessary to confirm or refute the findings of this review.

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Wetterslev 2008

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75.

Wetterslev 2009

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Medical Research Methodology* 2009;**9**:86.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aitola 1998

Methods	Randomised controlled trial.
Participants	Country: Finland. Number randomised: 40. Postrandomisation dropout: 1 (2.5%). Mean age: 48 years. Females: 32 (66.7%). ASA I or II: 40 (100%). ASA III or IV: 0 (0%). Inclusion criteria: • elective laparoscopic cholecystectomy; • people with symptomatic gallstones. Exclusion criteria:

Aitola 1998 *(Continued)*

	• people with suspected common bile duct stones.
Interventions	Pneumoperitoneum: 12-14 mmHg. Participants randomly assigned to 2 groups. Group 1: nitrous oxide pneumoperitoneum (n = 20). Group 2: carbon dioxide pneumoperitoneum (n = 20).
Outcomes	Complications, adverse events, cardiopulmonary changes (heart rate, blood pressure, blood pH, partial pressure of carbon dioxide, and mean end-tidal carbon dioxide), pain, analgesia requirements, operative time, and total gas volume.
Notes	1 postrandomisation dropout in nitrous oxide group. Reason for postrandomisation dropout: 1 participant developed a painful port-site rectus sheath haematoma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the nurse nor the patient knew which gas was used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The same anesthesiologist, who was blinded to the pneumoperitoneum gas used, took care of the anaesthesia of all the patients. The evaluation of postoperative pain was made on a double-blind, controlled basis by a trained nurse."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 1 postrandomisation dropout.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported. Some selective outcome reporting in secondary outcomes, but review authors considered this trial free of selective reporting for primary outcomes.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

Bongard 1993

Methods	Randomised controlled trial.
Participants	Country: USA. Number randomised: 20. Postrandomisation dropout: 1 (5%).

Bongard 1993 *(Continued)*

	Mean age: 34.4 years. Females: 17 (85%). ASA I or II: 20 (100%). ASA III or IV: 0 (0%). Inclusion criteria: • Elective laparoscopic cholecystectomy; • ASA I or II. Exclusion criteria: • aged > 55 years; • cardiopulmonary disease; • participation in another trial.
Interventions	Pneumoperitoneum: 15 mmHg. Participants randomly assigned to 2 groups. Group 1: helium pneumoperitoneum (n = 10). Group 2: carbon dioxide pneumoperitoneum (n = 10).
Outcomes	Complications, adverse events, cardiopulmonary changes (heart rate, blood pressure, blood pH, partial pressure of carbon dioxide, bicarbonate concentration, and end-tidal carbon dioxide), and duration of pneumoperitoneum.
Notes	1 postrandomisation dropout in helium group. Reason for postrandomisation dropout: conversion to open surgery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated code was used to randomise the insufflating agent used."
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The operating surgeon and anesthesiologist were informed of the randomisation result preoperatively."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Patient No. 9 (helium) was converted to an open procedure when the intraoperative cholangiogram showed multiple stones in a dilated common bile duct. The end values for this patient were recorded immediately before celiotomy incision at 110 minutes."

Bongard 1993 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported. Some selective outcome reporting in secondary outcomes, but review authors considered this trial free of selective reporting for primary outcomes.
Other bias	High risk	Quote: "The average weight of the helium group was significantly greater (P<0.02)."

Gu 2015

Methods	Randomised controlled trial.
Participants	Country: China. Number randomised: 146. Postrandomisation dropout: 0 (0%). Mean age: 44.7 years. Females: 83 (56.8%). ASA I or II: not mentioned. ASA III or IV: not mentioned. Inclusion criteria: • elective laparoscopic cholecystectomy; • people with gallstones or gallbladder polyps. Exclusion criteria: • people with surgical contraindication.
Interventions	Pneumoperitoneum: 12-14 mmHg. Participants randomly assigned to 2 groups. Group 1: room air pneumoperitoneum (n = 70). Group 2: carbon dioxide pneumoperitoneum (n = 76).
Outcomes	Complications, adverse events, cardiopulmonary changes (heart rate, blood pressure, partial pressure of carbon dioxide), pain, hospital costs, and duration of hospitalisation.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.

Gu 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported. Some selective outcome reporting in secondary outcomes, but review authors considered this trial free of selective reporting for primary outcomes.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

Lipscomb 1993

Methods	Randomised controlled trial.
Participants	Country: USA. Number randomised: 53. Postrandomisation dropout: 0 (0%). Mean age: 27.6 years. Females: 53 (100%). ASA I or II: not mentioned. ASA III or IV: not mentioned. Inclusion criteria: • elective laparoscopic tubal ligation. Exclusion criteria: not mentioned.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants randomly assigned to 2 groups. Group 1: nitrous oxide pneumoperitoneum (n = 29). Group 2: carbon dioxide pneumoperitoneum (n = 24).
Outcomes	Pain, analgesia requirements, and operative time.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Lipscomb 1993 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were prospectively randomised using computer-generated numbers."
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All data collection was by individuals blinded to the type of gas used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1 postrandomisation dropout.
Selective reporting (reporting bias)	High risk	Comment: none of primary outcomes reported.
Other bias	High risk	Quote: "There was a significant difference between the two groups in weight (P=0.004)."

Naude 1996

Methods	Randomised controlled trial.
Participants	Country: USA. Number randomised: 16. Postrandomisation dropout: 2 (12.5%). Mean age: 34.5 years. Females: 16 (100%). ASA I or II: not mentioned (%). ASA III or IV: not mentioned (%). Inclusion criteria: • elective laparoscopic cholecystectomy; • people with cholelithiasis. Exclusion criteria: not mentioned.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants randomly assigned to 2 groups. Group 1: helium pneumoperitoneum (n = 8). Group 2: carbon dioxide pneumoperitoneum (n = 8).

Naude 1996 *(Continued)*

Outcomes	Cardiopulmonary changes (blood pH and partial pressure of carbon dioxide), operative time, and hormone changes (e.g. adrenaline, noradrenaline, cortisol).
Notes	2 postrandomisation dropouts in carbon dioxide group. Reason for postrandomisation dropout: not mentioned. Main outcome in trial was hormone changes. Outcomes of interest for this review were blood pH and partial pressure of carbon dioxide.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The operating surgeon and the anesthesiologist were notified of the patient's assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 2 postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: none of the primary outcomes reported.
Other bias	High risk	Quote: "There was a significant age difference between the helium and CO_2 group."

Neuhaus 2001

Methods	Randomised controlled trial.
Participants	Country: Australia. Number randomised: 18. Postrandomisation dropout: 0. Mean age: not mentioned. Females: not mentioned. ASA I or II: not mentioned. ASA III or IV: not mentioned. Inclusion criteria:

Neuhaus 2001 *(Continued)*

- elective upper gastrointestinal laparoscopic surgery;
- people with gastro-oesophageal reflux disease or achalasia.

Exclusion criteria:

- people unable to provide informed consent;
- people undergoing reoperative antireflux surgery;
- people who had large (> 10 cm) hiatus hernias.

Interventions	Pneumoperitoneum: pressure not mentioned. Participants randomly assigned to 2 groups. Group 1: helium pneumoperitoneum (n = 8). Group 2: carbon dioxide pneumoperitoneum (n = 10).
Outcomes	Complications, adverse events, cardiopulmonary changes (blood pH and partial pressure of carbon dioxide), pain, analgesia requirements, operative time, and total gas volume.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Low risk	Quote: "All participants gave informed consent, and were randomised in the operating theatre by opening one of 20 previously sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The patients and the investigators were all blinded to which insufflation gas had been used."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients and the investigators were all blinded to which insufflation gas had been used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported. Some selective outcome reporting in secondary outcomes, but review authors considered this trial free of selective reporting for primary outcomes.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

O'Boyle 2002

Methods	Randomised controlled trial.
Participants	Country: Australia.

O'Boyle 2002 *(Continued)*

	Number randomised: 90 (to groups 1 and 2). Postrandomisation dropout: 6 (6.7%). Mean age: 49 years. Females: 58 (64%). ASA I or II: 82 (91.1%). ASA III or IV: 8 (8.9%). Inclusion criteria: • elective laparoscopic cholecystectomy or fundoplication. Exclusion criteria: • people unable to provide informed consent.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants (n = 173) were randomly assigned to 4 groups. Group 1: helium pneumoperitoneum (n = 43). Group 2: carbon dioxide pneumoperitoneum (n = 47). Group 3: carbon dioxide pneumoperitoneum with saline lavage (n = 43). We planned to combine groups to create a single pair-wise comparison for trials with multiple intervention groups. However, the saline lavage may decrease postoperative pain after laparoscopic surgery, which may be a confounding factor when we assess the effect of helium pneumoperitoneum on postoperative pain scores. Thus, this group was not included in the review. Group 4: helium pneumoperitoneum with saline lavage (n = 40). This group was also not included in the review.
Outcomes	Complications, adverse events, pain, analgesia requirements, operative time, hospital stay, and total gas volume.
Notes	There were 6 postrandomisation dropouts in the helium alone group. Reason for postrandomisation dropout: conversion to open surgery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by opening a sealed envelope for each patient in the operating theatre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The operating surgeon was not aware of the gas chosen until anaesthesia had commenced, and patients were blinded to the gas used throughout the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Post-operative assessment was also performed by a blinded investigator."

O'Boyle 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All data analysis was performed on an intention-to-treat basis. Where conversion to an open procedure was necessary, patients remained in their original allocated group."
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported. Some selective outcome reporting in secondary outcomes, but review authors considered this trial free of selective reporting for primary outcomes.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

Sietses 2002

Methods	Randomised controlled trial.
Participants	Country: Netherlands. Number randomised: 33. Postrandomisation dropout: 6 (18.2%). Mean age: 49 years. Females: not mentioned. ASA I or II: 33 (100%). ASA III or IV: 0 (0%). Inclusion criteria: • elective laparoscopic cholecystectomy. Exclusion criteria: • people with preoperative signs of acute cholecystitis or stones in the common bile duct.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants (n = 33) were randomly 3 groups. Group 1: helium pneumoperitoneum (n = not mentioned). Group 2: carbon dioxide pneumoperitoneum (n = not mentioned). Group 3: abdominal wall lift (n = not mentioned).
Outcomes	Peripheral white blood cell, C-reactive protein, interleukin-6, and HLA-DR (human leukocyte antigen - antigen D related) expression.
Notes	Reason for 6 postrandomisation dropouts: conversion to open surgery (n = 2, one from the helium group and one from the carbon dioxide group) and conversion from abdominal wall lift to carbon dioxide pneumoperitoneum (n = 4). All six excluded from the protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.

Sietses 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 6 postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: none of primary outcomes reported.
Other bias	Low risk	Comment: study appeared free of other sources of bias.

Tsereteli 2002

Methods	Randomised controlled trial.
Participants	Country: USA. Number randomised: 103. Postrandomisation dropout: 3 (2.8%). Mean age: 47.5 years. Females: 35 (45.5%). ASA I or II: 84 (84%). ASA III or IV: 16 (16%). Inclusion criteria: • elective laparoscopic surgery; • laparoscopic foregut surgery (Nissen fundoplication, Heller myotomy, and paraoesophageal hernia repair); • aged > 21 years. Exclusion criteria: not mentioned.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants randomly assigned to 2 groups. Group 1: nitrous oxide pneumoperitoneum (n = 51). Group 2: carbon dioxide pneumoperitoneum (n = 52).

Tsereteli 2002 *(Continued)*

Outcomes	Complications, adverse events, cardiopulmonary changes (heart rate, blood pressure, oxygen saturation, peak inspiratory pressure, mean end-tidal carbon dioxide, and mean minute ventilation), pain, analgesia requirements, operative time, duration of pneumoperitoneum, and hospital stay.
Notes	2 postrandomisation dropouts in carbon dioxide group. Reason for postrandomisation dropout: 1 participant was converted from laparoscopic surgery to laparotomy, and 1 participant demonstrated an oesophageal leak, which required thoracotomy to repair and extended hospital stay to 15 days. 1 postrandomisation dropout in nitrous oxide group. Reason for postrandomisation dropout: participant had repeat laparoscopy on postoperative day 1 because of herniation of fundoplication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomised after induction of general anaesthesia by an envelope drawing." Comment: not reported if the envelope was sealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients and anesthesiologists were blinded to the pneumoperitoneum gas used until the patient was discharged from the hospital."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Pain assessor (ZT) was blinded to the pneumoperitoneum gas used until the patient was discharged from the hospital."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 3 postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes reported. Some selective outcome reporting in secondary outcomes, but review authors considered this trial free of selective reporting for primary outcomes.
Other bias	Low risk	Comment: study appears free of other sources of bias.

ASA: American Society of Anesthesiologists; n: number of participants.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fernández-Cruz 1998	Non-randomised study.
Lipscomb 1994	Laparoscopic pelvic surgery performed by gynaecological surgeons under local anaesthesia.
McMahon 1994	Non-randomised study.

Study	Reason for exclusion
Neuberger 1996	Non-randomised study.
Ooka 1993	Non-randomised study.
Rammohan 2011	Non-randomised study.
Sharp 1982	Diagnostic laparoscopy performed under local anaesthesia.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bergstrom 2015

Methods	Randomised controlled trial?
Participants	Country: Sweden. Number of participants: 30. Mean age: not mentioned. Females: not mentioned. ASA I or II: not mentioned. ASA III or IV: not mentioned. Inclusion criteria: elective laparoscopic cholecystectomy. Exclusion criteria: not mentioned.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants randomly assigned to 2 groups. Group 1: helium pneumoperitoneum (n = 15). Group 2: carbon dioxide pneumoperitoneum (n = 15).
Outcomes	Peritoneal pH, peritoneal fibrinolytic components, and peritoneal fibrinolytic capacity.
Notes	Conference abstract. It needs further classification because we could not judge whether it is a true randomised controlled trial from the abstract.

Characteristics of ongoing studies *[ordered by study ID]*

Asgari 2012

Trial name or title	Prospective randomised trial comparing nitrous oxide and carbon dioxide for laparoscopic cholecystectomy.
Methods	Randomised controlled trial.
Participants	Country: Iran. Number of participants: 64.

Asgari 2012 *(Continued)*

	Inclusion criteria: • age < 65 years; • developed gallstones; • candidates for laparoscopic cholecystectomy; • written informed consent; • ASA I or II. Exclusion criteria: • signs and complications of gallstones in admission include acute cholecystitis and suppurative cholangitis; • complete inability to move; • severe physical or mental disorders leading to inability to communicate; • pregnancy and cancer.
Interventions	Pneumoperitoneum: pressure not mentioned. Participants randomly assigned to 2 groups. Group 1: nitrous oxide pneumoperitoneum. Group 2: carbon dioxide pneumoperitoneum.
Outcomes	Primary outcome heart rate. Secondary outcome mean arterial pressure.
Starting date	November 2010.
Contact information	Principal investigator: Mehdi Asgari, Ahvaz Jundishapur University of Medical Sciences, Iran.
Notes	

ASA: American Society of Anesthesiologists.

DATA AND ANALYSES

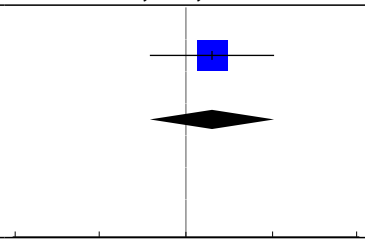
Comparison 1. Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	2	140	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.38, 10.43]
2 Procedure-related general complications	2	143	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.18, 5.71]
3 Analgesia requirements	3	193	Std. Mean Difference (IV, Random, 95% CI)	-0.69 [-1.42, 0.04]
3.1 Oxycodone (mg)	2	140	Std. Mean Difference (IV, Random, 95% CI)	-0.97 [-1.71, -0.22]
3.2 Ibuprofen (tablets/24 hours)	1	53	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.70, 0.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Cardiopulmonary changes	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Heart rate (beats/minute)	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-4.13, 2.93]
4.2 Mean arterial pressure (mmHg)	1	100	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-7.90, 0.30]
4.3 Oxygen saturation (%)	1	100	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.39, 0.39]
4.4 Peak airway pressure (cm H_2O)	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.17, 1.57]

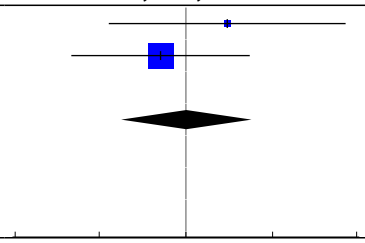
Analysis 1.1. Comparison 1 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 1 Cardiopulmonary complications.

Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aitola 1998	0/20	0/20			Not estimable
Tsereteli 2002	4/50	2/50		100%	2[0.38,10.43]
Total (95% CI)	**70**	**70**		**100%**	**2[0.38,10.43]**
Total events: 4 (Nitrous oxide), 2 (Carbon dioxide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					



Analysis 1.2. Comparison 1 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 2 Procedure-related general complications.

Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aitola 1998	1/20	0/20		20.16%	3[0.13,69.52]
Tsereteli 2002	1/51	2/52		79.84%	0.51[0.05,5.45]
Total (95% CI)	**71**	**72**		**100%**	**1.01[0.18,5.71]**
Total events: 2 (Nitrous oxide), 2 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=0.78, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					



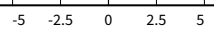
Analysis 1.3. Comparison 1 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 3 Analgesia requirements.

Study or subgroup	Nitrous oxide N	Nitrous oxide Mean(SD)	Carbon dioxide N	Carbon dioxide Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.3.1 Oxycodone (mg)							
Aitola 1998	20	12.6 (6.2)	20	16.8 (8.6)		31.17%	-0.55[-1.18,0.08]
Tsereteli 2002	50	53 (12.5)	50	69.5 (12.5)		35.59%	-1.31[-1.74,-0.88]
Subtotal ***	**70**		**70**			**66.76%**	**-0.97[-1.71,-0.22]**
Heterogeneity: Tau^2=0.21; Chi^2=3.78, df=1(P=0.05); I^2=73.54%							
Test for overall effect: Z=2.55(P=0.01)							
1.3.2 Ibuprofen (tablets/24 hours)							
Lipscomb 1993	29	1.8 (1.1)	24	2 (1.4)		33.24%	-0.16[-0.7,0.38]
Subtotal ***	**29**		**24**			**33.24%**	**-0.16[-0.7,0.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.57(P=0.57)							
Total ***	**99**		**94**			**100%**	**-0.69[-1.42,0.04]**
Heterogeneity: Tau^2=0.34; Chi^2=11.3, df=2(P=0); I^2=82.3%							
Test for overall effect: Z=1.85(P=0.06)							
Test for subgroup differences: Chi^2=2.97, df=1 (P=0.09), I^2=66.29%							

Favours nitrous oxide — Favours carbon dioxide

Analysis 1.4. Comparison 1 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 4 Cardiopulmonary changes.

Study or subgroup	Nitrous oxide N	Nitrous oxide Mean(SD)	Carbon dioxide N	Carbon dioxide Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.4.1 Heart rate (beats/minute)							
Tsereteli 2002	50	3.4 (8.9)	50	4 (9.1)		100%	-0.6[-4.13,2.93]
Subtotal ***	**50**		**50**			**100%**	**-0.6[-4.13,2.93]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.33(P=0.74)							
1.4.2 Mean arterial pressure (mmHg)							
Tsereteli 2002	50	6 (9.8)	50	9.8 (11.1)		100%	-3.8[-7.9,0.3]
Subtotal ***	**50**		**50**			**100%**	**-3.8[-7.9,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.81(P=0.07)							
1.4.3 Oxygen saturation (%)							
Tsereteli 2002	50	0.5 (1.1)	50	0.5 (0.9)		100%	0[-0.39,0.39]
Subtotal ***	**50**		**50**			**100%**	**0[-0.39,0.39]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.4.4 Peak airway pressure (cm H2O)							
Tsereteli 2002	50	5.6 (4.3)	50	5.9 (5.2)		100%	-0.3[-2.17,1.57]
Subtotal ***	**50**		**50**			**100%**	**-0.3[-2.17,1.57]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.31(P=0.75)							



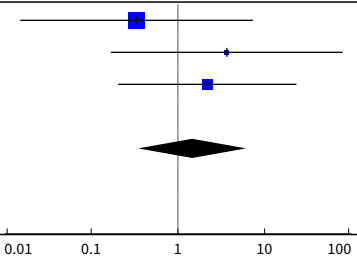
Favours nitrous oxide — Favours carbon dioxide

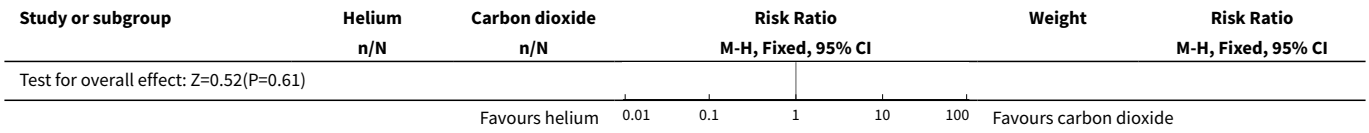
Comparison 2. Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	3	128	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.35, 6.12]
2 Pneumoperitoneum-related serious adverse events	3	128	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.28 [0.86, 80.03]
3 Pain scores (cm) (first postoperative day)	2	108	Mean Difference (IV, Fixed, 95% CI)	0.49 [-0.28, 1.26]
4 Analgesia requirements (morphine mg)	1	90	Mean Difference (IV, Fixed, 95% CI)	12.0 [4.44, 19.56]
5 Number of participants requiring analgesia	1	18	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.04]
6 Cardiopulmonary parameters	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Blood pH (start)	2	34	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.04]
6.2 Blood pH (middle)	3	52	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
6.3 Blood pH (end)	2	34	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.06, 0.14]
6.4 Partial pressure of carbon dioxide (mmHg) (start)	2	34	Mean Difference (IV, Fixed, 95% CI)	0.31 [-1.79, 2.40]
6.5 Partial pressure of carbon dioxide (mmHg) (middle)	3	52	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-3.70, 2.02]
6.6 Partial pressure of carbon dioxide (mmHg) (end)	2	34	Mean Difference (IV, Fixed, 95% CI)	-12.78 [-16.78, -8.77]

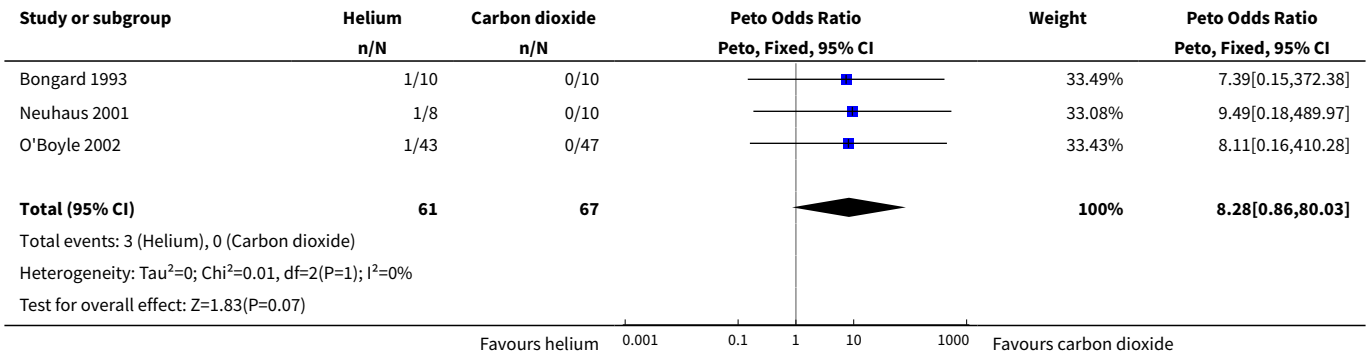
Analysis 2.1. Comparison 2 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 1 Cardiopulmonary complications.

Study or subgroup	Helium n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bongard 1993	0/10	1/10		51.63%	0.33[0.02,7.32]
Neuhaus 2001	1/8	0/10		15.49%	3.67[0.17,79.54]
O'Boyle 2002	2/43	1/47		32.89%	2.19[0.21,23.26]
Total (95% CI)	**61**	**67**		**100%**	**1.46[0.35,6.12]**
Total events: 3 (Helium), 2 (Carbon dioxide)					
Heterogeneity: Tau²=0; Chi²=1.33, df=2(P=0.51); I²=0%					

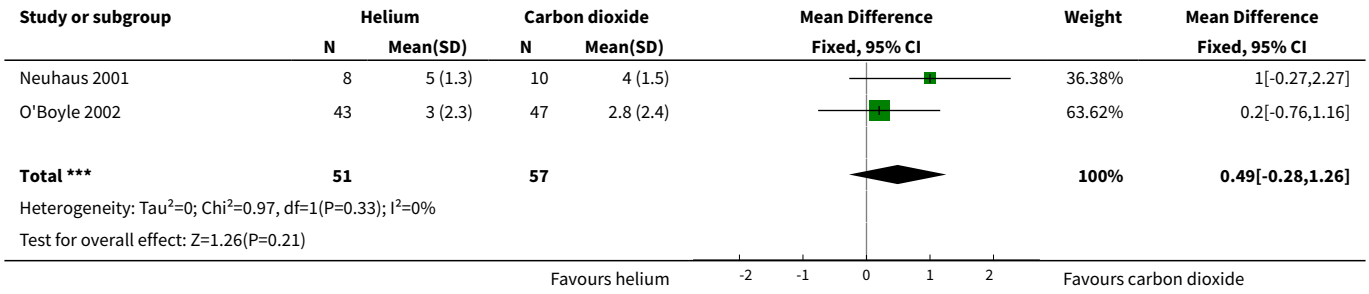




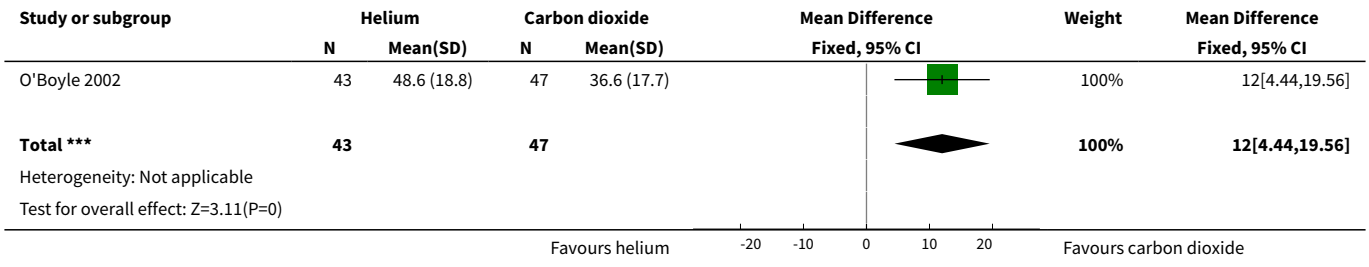
Analysis 2.2. Comparison 2 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 2 Pneumoperitoneum-related serious adverse events.



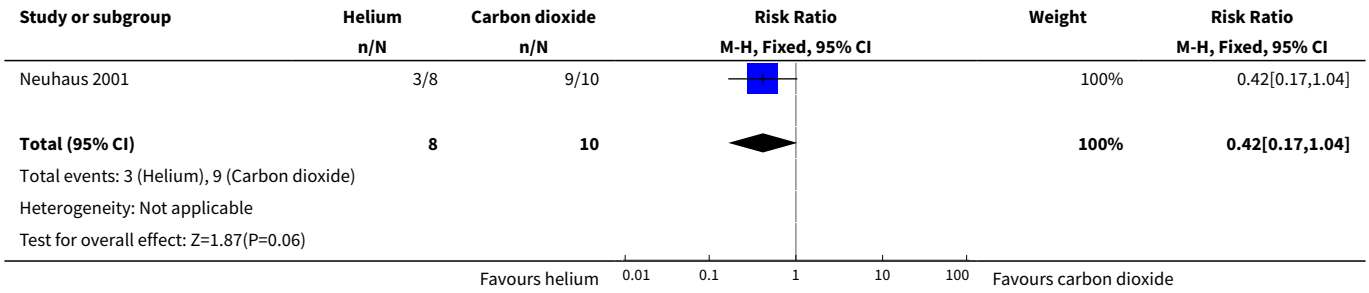
Analysis 2.3. Comparison 2 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 3 Pain scores (cm) (first postoperative day).



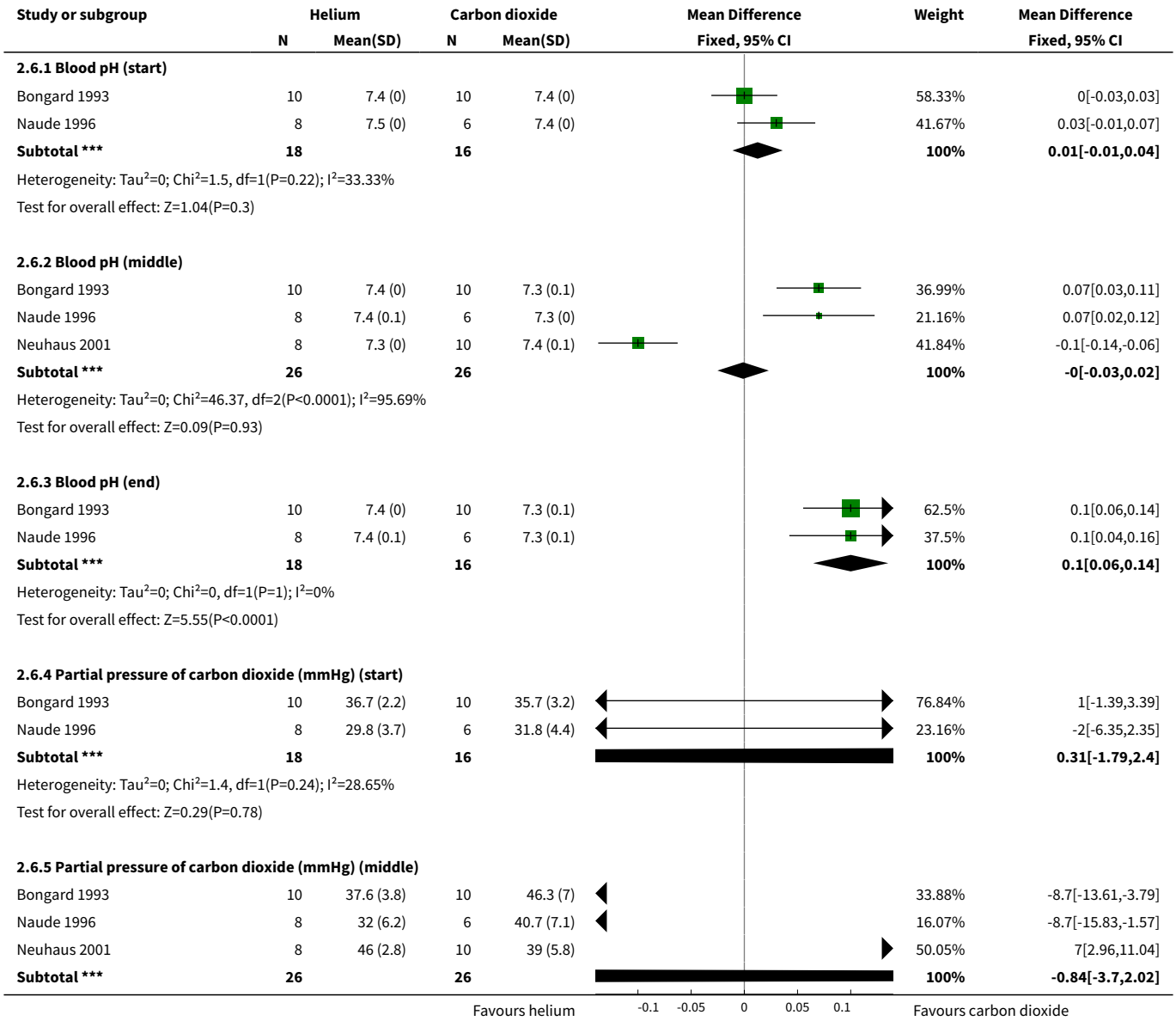
Analysis 2.4. Comparison 2 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 4 Analgesia requirements (morphine mg).

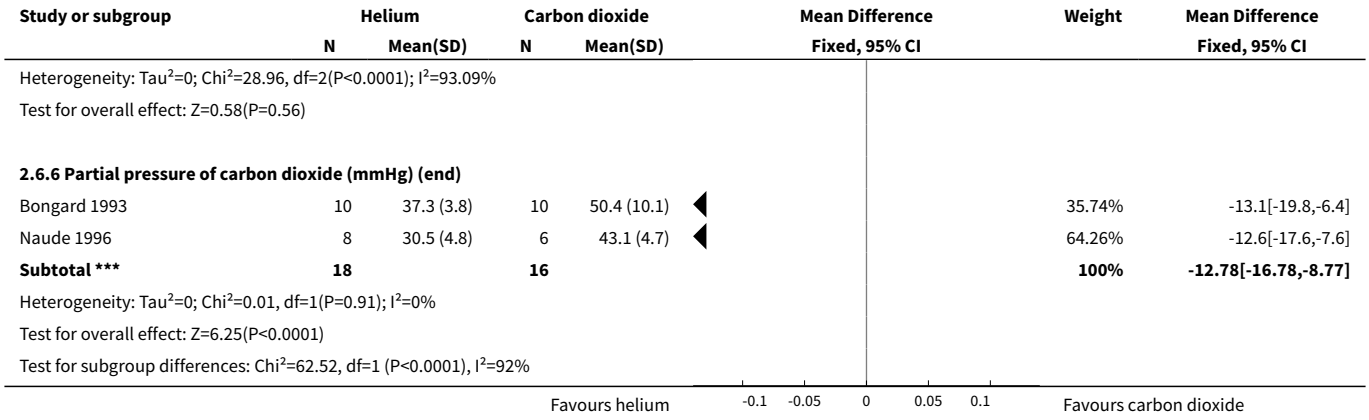


Analysis 2.5. Comparison 2 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 5 Number of participants requiring analgesia.



Analysis 2.6. Comparison 2 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 6 Cardiopulmonary parameters.





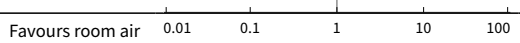
Comparison 3. Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pneumoperitoneum-related serious adverse events	1	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Pain scores (cm) (first postoperative day)	1	146	Mean Difference (IV, Fixed, 95% CI)	-0.8 [-1.15, -0.45]
4 Hospital costs (CNY)	1	146	Mean Difference (IV, Fixed, 95% CI)	-2667.0 [-3275.68, -2058.32]
5 Cardiopulmonary parameters	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Heart rate (beats/minute) (start)	1	146	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-3.11, 2.91]
5.2 Heart rate (beats/minute) (middle)	1	146	Mean Difference (IV, Fixed, 95% CI)	-7.30 [-9.78, -4.82]
5.3 Heart rate (beats/minute) (end)	1	146	Mean Difference (IV, Fixed, 95% CI)	-8.70 [-11.72, -5.68]
5.4 Blood systolic pressure (mmHg) (start)	1	146	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-5.12, 3.12]
5.5 Blood systolic pressure (mmHg) (middle)	1	146	Mean Difference (IV, Fixed, 95% CI)	2.80 [-0.44, 6.04]
5.6 Blood systolic pressure (mmHg) (end)	1	146	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.42, 1.42]
5.7 Partial pressure of carbon dioxide (mmHg) (start)	1	146	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.39, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.8 Partial pressure of carbon dioxide (mmHg) (middle)	1	146	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.37, 0.77]
5.9 Partial pressure of carbon dioxide (mmHg) (end)	1	146	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.43, 1.63]

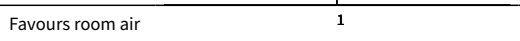
Analysis 3.1. Comparison 3 Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 1 Cardiopulmonary complications.

Study or subgroup	Room air n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gu 2015	0/70	0/76			Not estimable
Total (95% CI)	**70**	**76**			**Not estimable**
Total events: 0 (Room air), 0 (Carbon dioxide)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 3.2. Comparison 3 Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 2 Pneumoperitoneum-related serious adverse events.

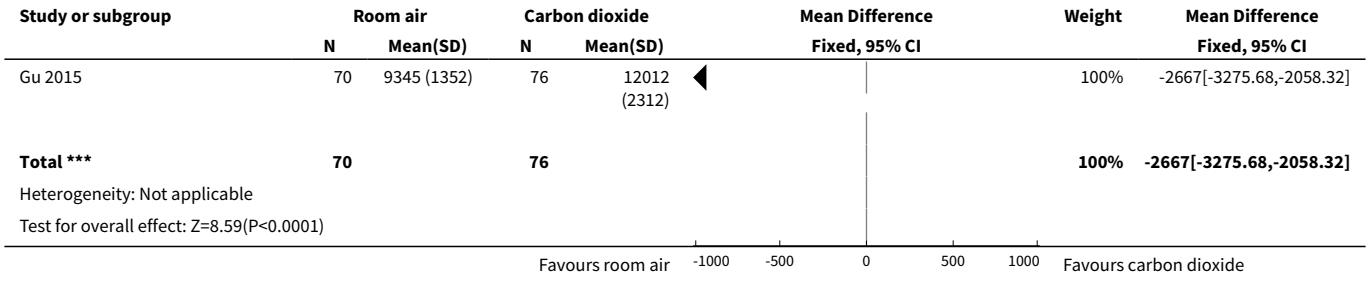
Study or subgroup	Room air n/N	Carbon dioxide n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gu 2015	0/70	0/76			Not estimable
Total (95% CI)	**70**	**76**			**Not estimable**
Total events: 0 (Room air), 0 (Carbon dioxide)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



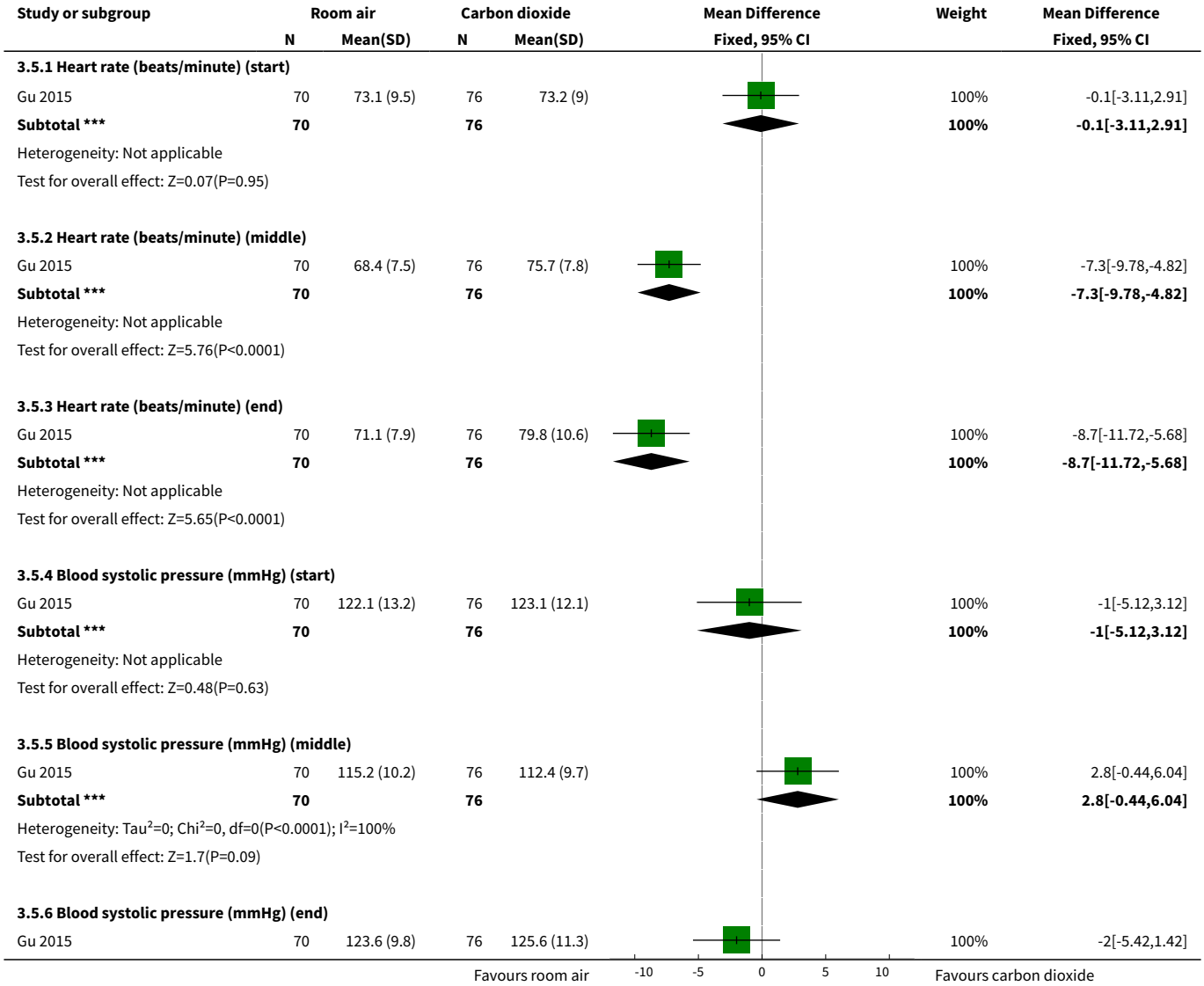
Analysis 3.3. Comparison 3 Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 3 Pain scores (cm) (first postoperative day).

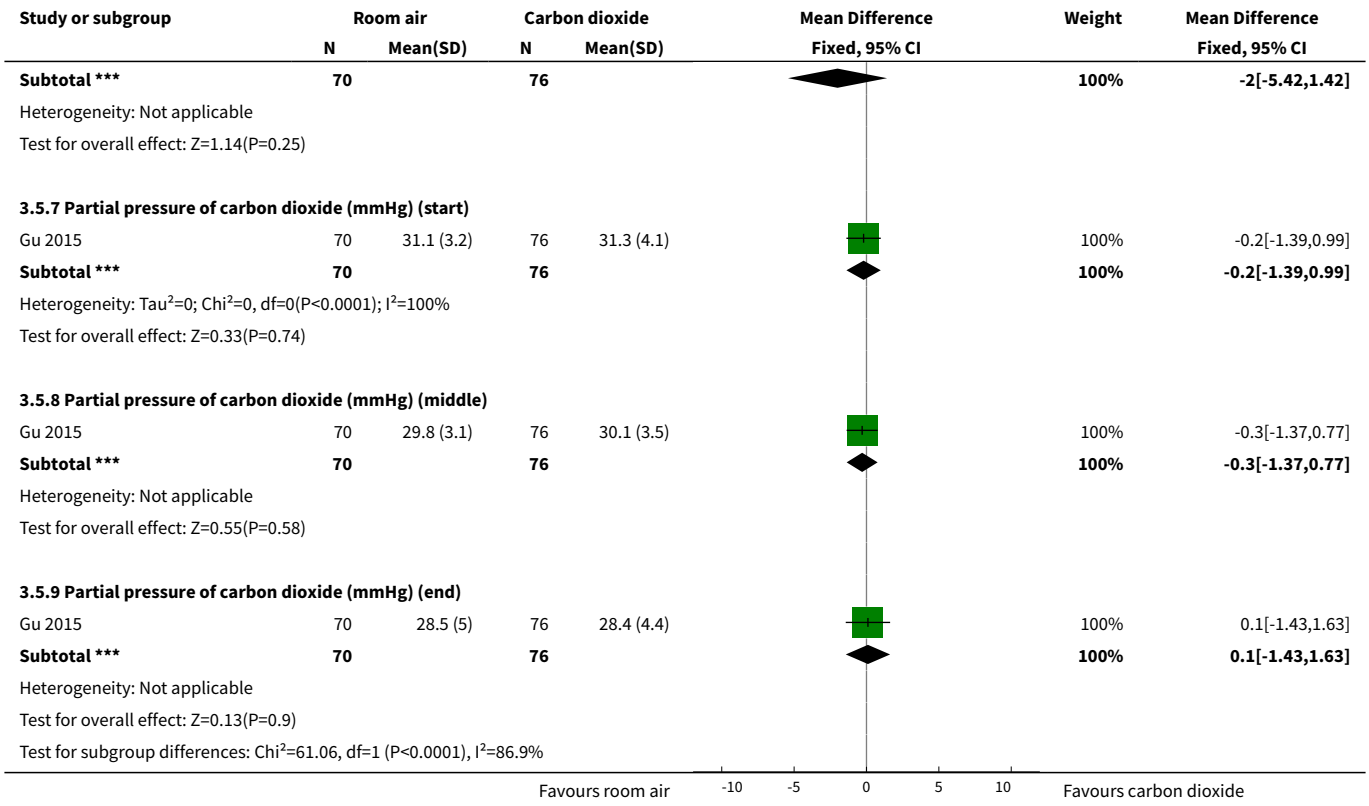
Study or subgroup	Room air N	Room air Mean(SD)	Carbon dioxide N	Carbon dioxide Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gu 2015	70	1.8 (0.8)	76	2.6 (1.3)		100%	-0.8[-1.15,-0.45]
Total ***	**70**		**76**			**100%**	**-0.8[-1.15,-0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.52(P<0.0001)							

Analysis 3.4. Comparison 3 Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 4 Hospital costs (CNY).



Analysis 3.5. Comparison 3 Room air pneumoperitoneum versus carbon dioxide pneumoperitoneum, Outcome 5 Cardiopulmonary parameters.





Comparison 4. Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	2	143	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [0.64, 10.93]
2 Procedure-related general complications	2	143	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.40, 8.31]
3 Pneumoperitoneum-related serious adverse events	2	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.46 [0.47, 119.30]
4 Mortality	2	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.46 [0.47, 119.30]

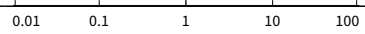
Analysis 4.1. Comparison 4 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 1 Cardiopulmonary complications.

Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aitola 1998	1/20	0/20		20.16%	3[0.13,69.52]
Tsereteli 2002	5/51	2/52		79.84%	2.55[0.52,12.55]
Total (95% CI)	**71**	**72**		**100%**	**2.64[0.64,10.93]**
Total events: 6 (Nitrous oxide), 2 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					

Favours nitrous oxide — Favours carbon dioxide

Analysis 4.2. Comparison 4 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 2 Procedure-related general complications.

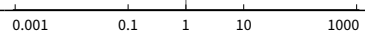
Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aitola 1998	2/20	0/20		20.16%	5[0.26,98]
Tsereteli 2002	2/51	2/52		79.84%	1.02[0.15,6.97]
Total (95% CI)	**71**	**72**		**100%**	**1.82[0.4,8.31]**
Total events: 4 (Nitrous oxide), 2 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=0.79, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.77(P=0.44)					



Favours nitrous oxide — Favours carbon dioxide

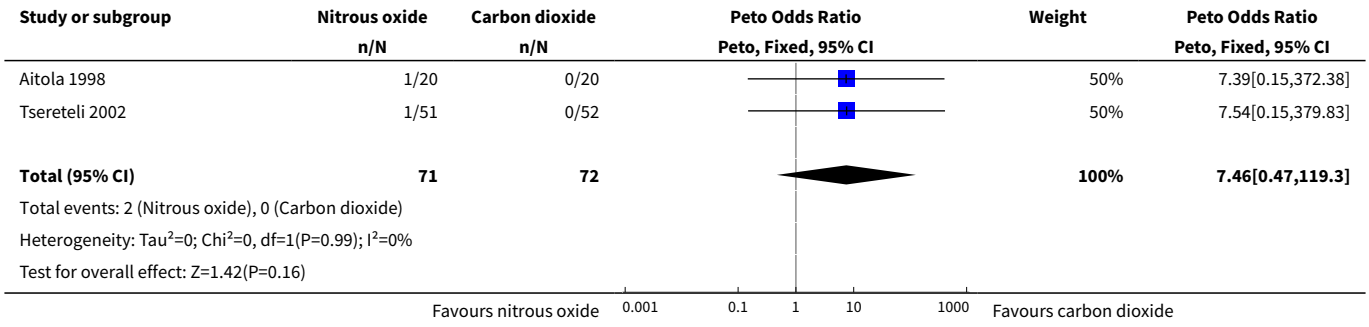
Analysis 4.3. Comparison 4 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 3 Pneumoperitoneum-related serious adverse events.

Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aitola 1998	1/20	0/20		50%	7.39[0.15,372.38]
Tsereteli 2002	1/51	0/52		50%	7.54[0.15,379.83]
Total (95% CI)	**71**	**72**		**100%**	**7.46[0.47,119.3]**
Total events: 2 (Nitrous oxide), 0 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=1.42(P=0.16)					



Favours nitrous oxide — Favours carbon dioxide

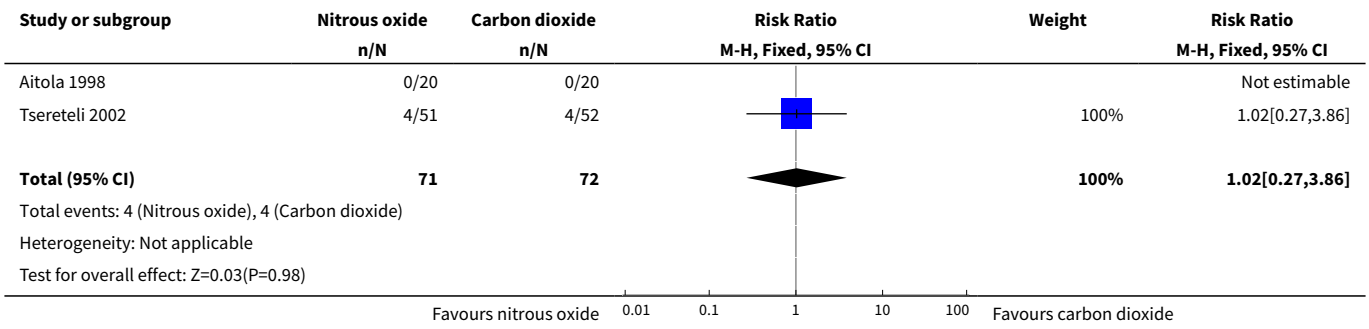
Analysis 4.4. Comparison 4 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 4 Mortality.



Comparison 5. Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	2	143	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.27, 3.86]
2 Procedure-related general complications	2	143	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.12, 2.58]
3 Pneumoperitoneum-related serious adverse events	2	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.19]
4 Mortality	2	143	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.19]

Analysis 5.1. Comparison 5 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 1 Cardiopulmonary complications.



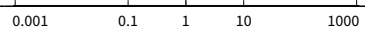
Analysis 5.2. Comparison 5 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 2 Procedure-related general complications.

Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aitola 1998	1/20	0/20		11.21%	3[0.13,69.52]
Tsereteli 2002	1/51	4/52		88.79%	0.25[0.03,2.2]
Total (95% CI)	**71**	**72**		**100%**	**0.56[0.12,2.58]**
Total events: 2 (Nitrous oxide), 4 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=1.61, df=1(P=0.2); I^2=37.77%					
Test for overall effect: Z=0.74(P=0.46)					

Favours nitrous oxide — Favours carbon dioxide

Analysis 5.3. Comparison 5 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 3 Pneumoperitoneum-related serious adverse events.

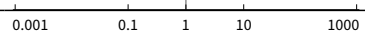
Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aitola 1998	0/20	0/20			Not estimable
Tsereteli 2002	0/51	2/52		100%	0.14[0.01,2.19]
Total (95% CI)	**71**	**72**		**100%**	**0.14[0.01,2.19]**
Total events: 0 (Nitrous oxide), 2 (Carbon dioxide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					



Favours nitrous oxide — Favours carbon dioxide

Analysis 5.4. Comparison 5 Nitrous oxide pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 4 Mortality.

Study or subgroup	Nitrous oxide n/N	Carbon dioxide n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aitola 1998	0/20	0/20			Not estimable
Tsereteli 2002	0/51	2/52		100%	0.14[0.01,2.19]
Total (95% CI)	**71**	**72**		**100%**	**0.14[0.01,2.19]**
Total events: 0 (Nitrous oxide), 2 (Carbon dioxide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					



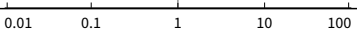
Favours nitrous oxide — Favours carbon dioxide

Comparison 6. Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	3	128	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [1.21, 17.36]
2 Procedure-related general complications	4	144	Risk Ratio (M-H, Fixed, 95% CI)	8.47 [1.11, 64.60]
3 Pneumoperitoneum-related serious adverse events	3	128	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.19 [2.56, 33.01]
4 Mortality	4	144	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.89 [1.94, 40.64]

Analysis 6.1. Comparison 6 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 1 Cardiopulmonary complications.

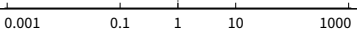
Study or subgroup	Helium n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bongard 1993	1/10	1/10		41.57%	1[0.07,13.87]
Neuhaus 2001	1/8	0/10		18.71%	3.67[0.17,79.54]
O'Boyle 2002	8/43	1/47		39.72%	8.74[1.14,67.07]
Total (95% CI)	**61**	**67**		**100%**	**4.58[1.21,17.36]**
Total events: 10 (Helium), 2 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=1.69, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=2.23(P=0.03)					



Favours helium — Favours carbon dioxide

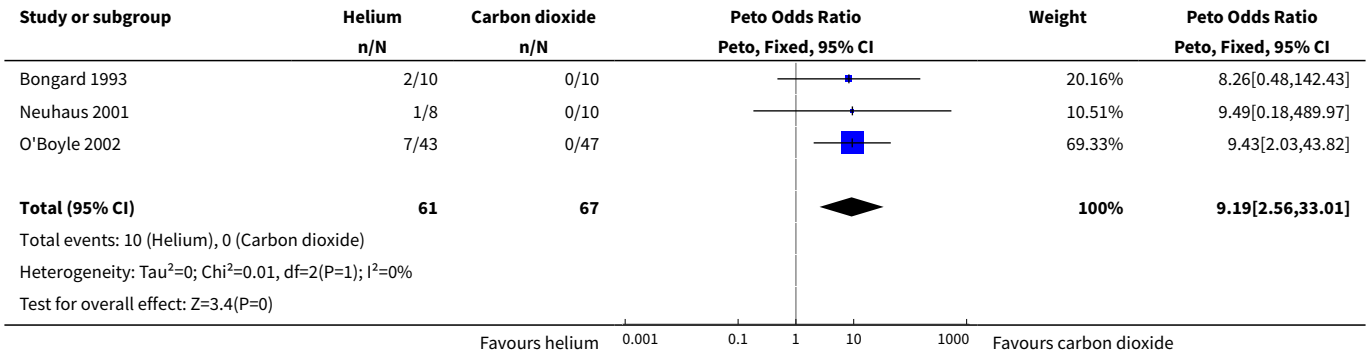
Analysis 6.2. Comparison 6 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 2 Procedure-related general complications.

Study or subgroup	Helium n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bongard 1993	1/10	0/10		51.11%	3[0.14,65.9]
Naude 1996	0/8	0/8			Not estimable
Neuhaus 2001	0/8	0/10			Not estimable
O'Boyle 2002	6/43	0/47		48.89%	14.18[0.82,244.49]
Total (95% CI)	**69**	**75**		**100%**	**8.47[1.11,64.6]**
Total events: 7 (Helium), 0 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=2.06(P=0.04)					

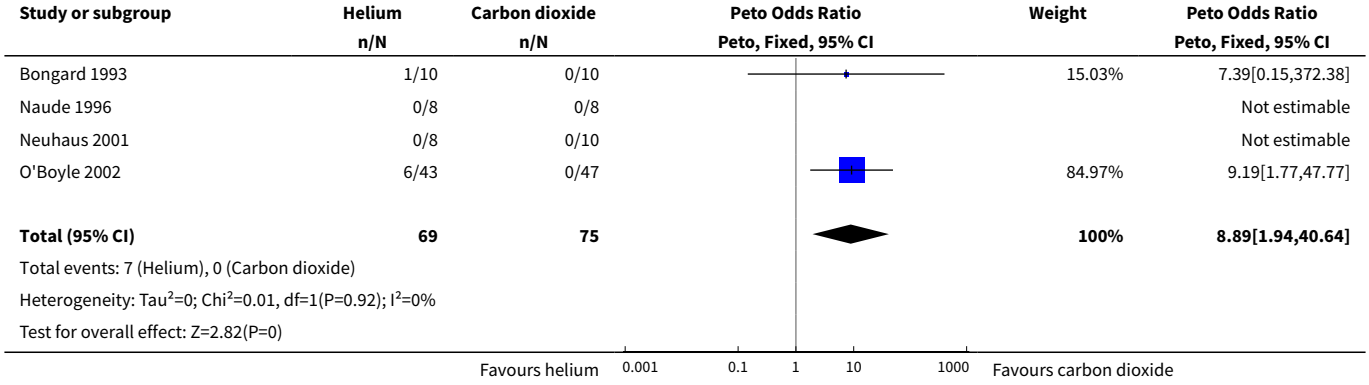


Favours helium — Favours carbon dioxide

Analysis 6.3. Comparison 6 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 3 Pneumoperitoneum-related serious adverse events.



Analysis 6.4. Comparison 6 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (worst/best-case scenario analysis for missing data), Outcome 4 Mortality.

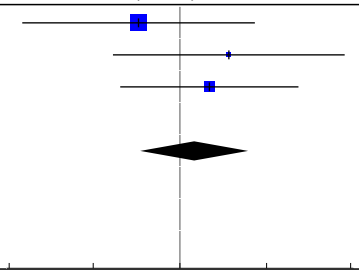


Comparison 7. Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiopulmonary complications	3	128	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.35, 6.12]
2 Procedure-related general complications	4	144	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.61]
3 Pneumoperitoneum-related serious adverse events	3	128	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.28 [0.86, 80.03]
4 Mortality	4	144	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.01, 2.07]

Analysis 7.1. Comparison 7 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 1 Cardiopulmonary complications.

Study or subgroup	Helium n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bongard 1993	0/10	1/10		51.63%	0.33[0.02,7.32]
Neuhaus 2001	1/8	0/10		15.49%	3.67[0.17,79.54]
O'Boyle 2002	2/43	1/47		32.89%	2.19[0.21,23.26]
Total (95% CI)	**61**	**67**		**100%**	**1.46[0.35,6.12]**
Total events: 3 (Helium), 2 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=1.33, df=2(P=0.51); I^2=0%					
Test for overall effect: Z=0.52(P=0.61)					



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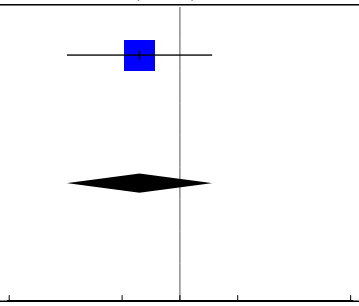
Analysis 7.2. Comparison 7 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 2 Procedure-related general complications.

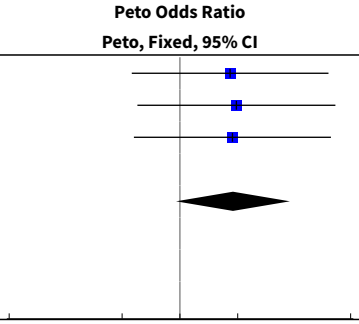
Study or subgroup	Helium n/N	Carbon dioxide n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bongard 1993	0/10	0/10			Not estimable
Naude 1996	0/8	2/8		100%	0.2[0.01,3.61]
Neuhaus 2001	0/8	0/10			Not estimable
O'Boyle 2002	0/43	0/47			Not estimable
Total (95% CI)	**69**	**75**		**100%**	**0.2[0.01,3.61]**
Total events: 0 (Helium), 2 (Carbon dioxide)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.28)					



Favours helium — Favours carbon dioxide

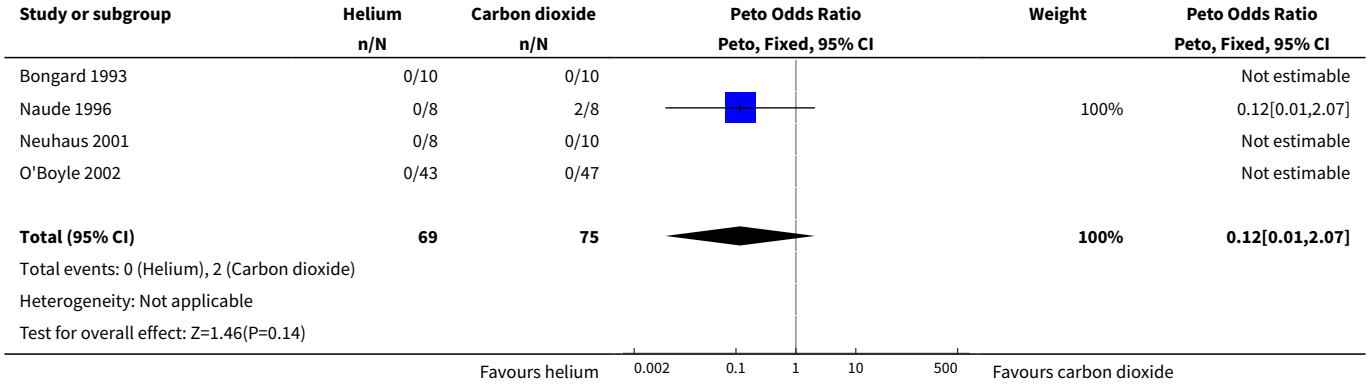
Analysis 7.3. Comparison 7 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 3 Pneumoperitoneum-related serious adverse events.

Study or subgroup	Helium n/N	Carbon dioxide n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bongard 1993	1/10	0/10		33.49%	7.39[0.15,372.38]
Neuhaus 2001	1/8	0/10		33.08%	9.49[0.18,489.97]
O'Boyle 2002	1/43	0/47		33.43%	8.11[0.16,410.28]
Total (95% CI)	**61**	**67**		**100%**	**8.28[0.86,80.03]**
Total events: 3 (Helium), 0 (Carbon dioxide)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=2(P=1); I^2=0%					
Test for overall effect: Z=1.83(P=0.07)					



Favours helium — Favours carbon dioxide

Analysis 7.4. Comparison 7 Helium pneumoperitoneum versus carbon dioxide pneumoperitoneum (best/worst-case scenario analysis for missing data, Outcome 4 Mortality.



ADDITIONAL TABLES

Table 1. Sensitivity analysis by changing between worst-case scenario analysis and best-case scenario analysis for missing data

Changing between worst-case scenario analysis and best-case scenario analysis for missing data			
Outcomes	**Risk ratio (95% CI)**		
	Main analysis	**Worst/best-case**	**Best/worst-case**
Cardiopulmonary complications (nitrous oxide vs carbon dioxide)	2.00 (0.38, 10.43)	2.64 (0.64, 10.93)	1.02 (0.27, 3.86)
Procedure-related general complications/surgical morbidity (nitrous oxide vs carbon dioxide)	1.01 (0.18, 5.71)	1.82 (0.40, 8.31)	0.56 (0.12, 2.58)
Pneumoperitoneum-related serious adverse events (nitrous oxide vs carbon dioxide)	No events	Peto OR 7.46 (0.47, 119.30)	Peto OR 0.14 (0.01, 2.19)
Mortality (nitrous oxide vs carbon dioxide)	No events	Peto OR 7.46 (0.47, 119.30)	Peto OR 0.14 (0.01, 2.19)
Cardiopulmonary complications (helium vs carbon dioxide)	1.46 (0.35, 6.12)	4.58 (1.21, 17.36)	1.46 (0.35, 6.12)
Procedure-related general complications/surgical morbidity (helium vs carbon dioxide)	No events	8.47 (1.11, 64.60)	0.20 (0.01, 3.61)
Pneumoperitoneum-related serious adverse events (helium vs carbon dioxide)	Peto OR 8.28 (0.86, 80.03)	Peto OR 9.19 (2.56, 33.01)	Peto OR 8.28 (0.86, 80.03)
Mortality (helium vs carbon dioxide)	No events	Peto OR 8.89 (1.94, 40.64)	Peto OR 0.12 (0.01, 2.07)

Peto OR: Peto odds ratio, which was calculated for rare events (mortality, serious adverse events).

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 MeSH descriptor: [Surgical Procedures, Minimally Invasive] explode all trees

#2 MeSH descriptor: [Laparoscopy] explode all trees

#3 MeSH descriptor: [Video-Assisted Surgery] explode all trees

#4 (laparoscop* or coelioscop* or celioscop* or peritoneoscop* or minimally invasive or video assisted surgery)

#5 (#1 or #2 or #3 or #4)

#6 MeSH descriptor: [Carbon Dioxide] explode all trees

#7 MeSH descriptor: [Nitrogen Oxides] explode all trees

#8 MeSH descriptor: [Nitrogen] explode all trees

#9 MeSH descriptor: [Argon] explode all trees

#10 MeSH descriptor: [Helium] explode all trees

#11 (gas* or carbon dioxide or CO2 or nitrous oxide or laughing gas or N2O or nitrogen or N2 or helium or argon)

#12 (#6 or #7 or #8 or #9 or #10 or #11)

#13 MeSH descriptor: [Pneumoperitoneum] explode all trees

#14 (pneumoperitoneum*)

#15 (#13 or #14)

#16 (#5 and #12 and #15)

Appendix 2. MEDLINE (Ovid) search strategy

1. exp Surgical Procedures, Minimally Invasive/

2. exp Laparoscopy/

3. exp Video-Assisted Surgery/

4. (laparoscop* or coelioscop* or celioscop* or peritoneoscop* or minimally invasive or video assisted surgery).mp.

5. 1 or 2 or 3 or 4

6. exp Carbon Dioxide/

7. exp Nitrogen Oxides/

8. exp Nitrogen/

9. exp Argon/

10. exp Helium/

11. (gas* or carbon dioxide or CO2 or nitrous oxide or laughing gas or N2O or nitrogen or N2 or helium or argon).mp.

12. 6 or 7 or 8 or 9 or 10 or 11

13. exp Pneumoperitoneum/

14. pneumoperitoneum*.mp.

15. 13 or 14

16. 5 and 12 and 15

17. randomized controlled trial.pt.

18. controlled clinical trial.pt.

19. randomized.ab.

20. placebo.ab.

21. clinical trial as topic.sh.

22. randomly.ab.

23. trial.ti.

24. 17 or 18 or 19 or 20 or 21 or 22 or 23

25. exp animals/ not humans.sh.

26. 24 not 25

27. 16 and 26

Appendix 3. Embase (Ovid) search strategy

1. exp minimally invasive surgery/

2. exp laparoscopy/

3. (laparoscop* or coelioscop* or celioscop* or peritoneoscop* or minimally invasive or video assisted surgery).mp.

4. 1 or 2 or 3

5. exp carbon dioxide/

6. exp nitrous oxide/

7. exp nitrogen/

8. exp argon/

9. exp helium/

10. exp gas/

11. (gas* or carbon dioxide or CO2 or nitrous oxide or laughing gas or N2O or nitrogen or N2 or helium or argon).mp.

12. 5 or 6 or 7 or 8 or 9 or 10 or 11

13. exp pneumoperitoneum/

14. pneumoperitoneum*.mp.

15. 13 or 14

16. 4 and 12 and 15

17. CROSSOVER PROCEDURE.sh

18. DOUBLE-BLIND PROCEDURE.sh

19. SINGLE-BLIND PROCEDURE.sh

20. (crossover* or cross over*).ti,ab.

21. placebo*.ti,ab.

22. (doubl* adj blind*).ti,ab.

23. allocate*.ti,ab.

24. trial.ti.

25. RANDOMIZED CONTROLLED TRIAL.sh.

26. random*.ti,ab.

27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. (exp animal/ or exp invertebrate/ or animal.hw or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)

29. 27 not 28

30. 16 and 29

Appendix 4. Science Citation Index Expanded search strategy

#1 Topic=(laparoscop* or coelioscop* or celioscop* or peritoneoscop* or minimally invasive or video assisted surgery)

#2 Topic=(gas* or carbon dioxide or CO2 or nitrous oxide or laughing gas or N2O or nitrogen or N2 or helium or argon)

#3 Topic=(pneumoperitoneum*)

#4 Topic=(randomized or randomised or controlled or trial or clinical or placebo or clinical or randomly or trial)

#5 (#4 AND #3 AND #2 AND #1)

Appendix 5. Criteria for judging risk of bias in the 'Risk of bias' assessment tool

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.	
Criteria for a judgement of 'Low risk' of bias.	The investigators described a random component in the sequence generation process such as: • referring to a random number table; • using a computer random number generator; • coin tossing; • shuffling cards or envelopes; • throwing dice; • drawing of lots; • minimisation.* *Minimisation may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of 'High risk' of bias.	The investigators described a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, e.g.: • sequence generated by odd or even date of birth; • sequence generated by some rule based on date (or day) of admission; • sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, e.g.: • allocation by judgement of the clinician;

(Continued)

	• allocation by preference of the participant; • allocation based on the results of a laboratory test or a series of tests; • allocation by availability of the intervention.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk.'

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Criteria for a judgement of 'Low risk' of bias.	Participants and investigators enrolling participants could not have foreseen assignment because 1 of the following, or an equivalent method, was used to conceal allocation: • central allocation (including telephone, web-based and pharmacy-controlled randomisation); • sequentially numbered drug containers of identical appearance; • sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'High risk' of bias.	Participants or investigators enrolling participants could possibly have foreseen assignments and thus introduced selection bias, such as allocation based on: • using an open random allocation schedule (e.g. a list of random numbers); • assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • alternation or rotation; • date of birth; • case record number; • any other explicitly unconcealed procedure.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk.' This is usually the case if the method of concealment was not described or not described in sufficient detail to allow a definite judgement; e.g. if the use of assignment envelopes was described, but it remained unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Criteria for a judgement of 'Low risk' of bias.	Any 1 of the following: • no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by lack of blinding; • blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any 1 of the following: • no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; • blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any 1 of the following: • insufficient information to permit judgement of 'Low risk' or 'High risk;' • study did not address this outcome.

Blinding of outcome assessment

(Continued)

Detection bias due to knowledge of the allocated interventions by outcome assessors.

Criteria for a judgement of 'Low risk' of bias.	Any 1 of the following: • no blinding of outcome assessment, but the review authors judged that the outcome measurement was not likely to be influenced by lack of blinding; • blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'High risk' of bias.	Any 1 of the following: • no blinding of outcome assessment, and the outcome measurement was likely to be influenced by lack of blinding; • blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.
Criteria for the judgement of 'Unclear risk' of bias.	Any 1 of the following: • insufficient information to permit judgement of 'Low risk' or 'High risk;' • study did not address this outcome.

Incomplete outcome data

Attrition bias due to amount, nature, or handling of incomplete outcome data.

Criteria for a judgement of 'Low risk' of bias.	Any 1 of the following: • no missing outcome data; • reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • missing data were imputed using appropriate methods.
Criteria for the judgement of 'High risk' of bias.	Any 1 of the following: • reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; • potentially inappropriate application of simple imputation.
Criteria for the judgement of 'Unclear risk' of bias.	Any 1 of the following: • insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomised not stated, no reasons for missing data provided); • study did not address this outcome.

Selective reporting

(Continued)

Reporting bias due to selective outcome reporting.

Criteria for a judgement of 'Low risk' of bias.	Any of the following: • study protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way; • study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'High risk' of bias.	Any 1 of the following: • not all of the study's prespecified primary outcomes were reported; • ≥ 1 primary outcomes weres reported using measurements, analysis methods, or subsets of data (e.g. subscales) that were not prespecified; • ≥ 1 reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); • ≥ 1 outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; • study report did not include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk.' It is likely that the majority of studies will fall into this category.

Other bias

Bias due to problems not covered elsewhere in the table.

Criteria for a judgement of 'Low risk' of bias.	Study appeared to be free of other sources of bias.
Criteria for the judgement of 'High risk' of bias.	There was ≥ 1 important risk of bias; e.g. the study: • had a potential source of bias related to the specific study design used; or • was claimed to have been fraudulent; or • had some other problem.
Criteria for the judgement of 'Unclear risk' of bias.	There may be a risk of bias, but there was either: • insufficient information to assess whether an important risk of bias existed; or • insufficient rationale or evidence that an identified problem would introduce bias.

WHAT'S NEW

Date	Event	Description
14 June 2017	New citation required but conclusions have not changed	Updated review with one additional new randomised controlled trial included.

CONTRIBUTIONS OF AUTHORS

YC: drafted the protocol and drafted the final review.

XW: study selection; risk of bias assessment of the included trials.

BT: study selection; risk of bias assessment of the included trials.

NC: data extraction; entered data into Review Manager 5; carried out the analysis.

JG: data extraction; entered data into Review Manager 5, and revised the final review.

YT: drafted and revised the final review; study selection; data extraction.

LB: revised the final review; data extraction; secured funding for the review.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- The Second Affiliated Hospital, Chongqing Medical University, China.
- West China Hospital, Sichuan University, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We applied the trial sequential analysis (TSA) approach for improving the reliability of conclusions, which we had not stated in the protocol.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Air; *Carbon Dioxide [adverse effects]; *Helium [adverse effects]; *Nitrous Oxide [adverse effects]; Abdomen [*surgery]; Analgesia [statistics & numerical data]; Laparoscopy [*methods]; Pneumoperitoneum, Artificial [adverse effects] [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans